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(54) Title: CHIMPANZEE ADENOVIRUS VECTORS

(57) Abstract

A recombinant vector comprises chimpanzee adenovirus sequences and a heterologous gene under the control of regulatory sequences. A cell line which expresses chimpanzee adenovirus gene(s) is also disclosed. Methods of using the vectors and cell lines are provided.

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CHIMPANZEE ADENOVIRUS VECTORS

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Field of the Invention

The present invention relates to the field of vectors useful in somatic gene therapy and the production and use thereof, and also to the field of vaccines.

Background of the Invention

I. Gene Therapy

Gene therapy is an approach to treating disease, generally human disease, that is based on the modification of gene expression in cells of the patient. It has become apparent over the last decade that the single most outstanding barrier to the success of gene therapy as a strategy for treating inherited diseases, cancer, and other genetic dysfunctions is the development of useful gene transfer vehicles.

Eukaryotic viruses have been employed as vehicles for somatic gene therapy. Among the viral vectors that have been cited frequently in gene therapy research are adenoviruses. Adenoviruses are eukaryotic DNA viruses that can be modified to efficiently deliver a therapeutic or reporter transgene to a variety of cell types. Human adenoviruses are composed of a linear, approximately 36 kb double-stranded DNA genome, which is divided into 100 map units (m.u.), each of which is 360 bp in length. The DNA contains short inverted terminal repeats (ITR) at each end of the genome that are required for viral DNA replication. The gene products are organized into early (E1 through E4) and late (L1 through L5) regions, based on expression before or after the initiation of viral DNA synthesis [see, e.g., Horwitz,

Virology, 2d edit., ed. B. N. Fields, Raven Press, Ltd., New York (1990)].

Recombinant adenoviruses types 2 and 5 (Ad2 and Ad5, respectively), which cause respiratory disease in humans, are currently being developed for gene therapy. Both Ad2 and Ad5 belong to a subclass of adenovirus and are not associated with human malignancies.

Recombinant adenoviruses are capable of providing extremely high levels of transgene delivery to virtually all cell types, regardless of the mitotic state. High titers (10^{13} plaque forming units/ml) of recombinant virus can be easily generated in an adenovirus-transformed, human embryonic kidney cell line 293 [ATCC CRL1573]. The 293 cell line contains a functional adenovirus E1a gene which provides a transacting E1a protein. It can be cryo-stored for extended periods without appreciable losses.

The efficacy of this system in delivering a therapeutic transgene *in vivo* that complements a genetic imbalance has been demonstrated in animal models of various disorders [K. F. Kozarsky et al, Somatic Cell Mol. Genet., 19:449-458 (1993) ("Kozarsky et al I"); K. F. Kozarsky et al, J. Biol. Chem., 269:13695-13702 (1994) ("Kozarsky et al II); Y. Watanabe, Atherosclerosis, 36:261-268 (1986); K. Tanzawa et al, FEBS Letters, 118(1):81-84 (1980); J.L. Golasten et al, New Engl. J. Med., 309:288-296 (1983); S. Ishibashi et al, J. Clin. Invest., 92:883-893 (1993); and S. Ishibashi et al, J. Clin. Invest., 93:1885-1893 (1994)]. Indeed, a recombinant replication defective adenovirus encoding a cDNA for the cystic fibrosis transmembrane regulator (CFTR) has been approved for use in at least two human CF clinical trials [see, e.g., J. Wilson, Nature, 365:691-692 (Oct. 21, 1993)]. The use of adenovirus vectors in

the transduction of genes into hepatocytes *in vivo* has previously been demonstrated in rodents and rabbits [see, e.g., Kozarsky II, cited above, and S. Ishibashi et al, J. Clin. Invest., 92:883-893 (1993)]. Further support of the safety of recombinant adenoviruses for gene therapy is the extensive experience of live adenovirus vaccines in human populations.

However, many humans have pre-existing immunity to human adenoviruses as a result of previous natural exposure, and this immunity is a major obstacle to the use of recombinant human adenoviruses for gene therapy protocols.

II. Vaccines

Replication competent, recombinant adenovirus (Ad) containing a variety of inserted genes have been used as vaccine compositions with some success [see, e.g. Davis, U.S. Patent No. 4,920,309]. Others have described the insertion of a foreign gene into a live [L. Prevac, J. Infect. Dis., 161:27-30 (1990)] and a replication-defective adenovirus for putative use as a vaccine [See, e.g. T. Ragot et al, J. Gen. Virol., 74:501-507 (1993); M. Eliot et al, J. Gen. Virol., 71:2425-2431 (1990); and S. C. Jacobs et al, J. Virol., 66:2086-2095 (1992)]. Jacobs et al, cited above, describes a recombinant E1-deleted, E3 intact, Ad containing encephalitis virus protein NS1 under the control of a heterologous cytomegalovirus (CMV) promoter. When mice were immunized with the recombinant Ad vaccines and challenged with virus, Jacobs et al obtained partial protection (at most a 75% protection) for an average survival of 15 days. Eliot et al, cited above, describe a recombinant E1-deleted, partially E3-deleted Ad with pseudorabies glycoprotein 50 inserted into the E1 deletion site under the control of a homologous Ad promoter. In rabbits and mice, after immunization and

challenge, only partial protection was obtained (i.e., about one-third). Ragot et al, cited above, describe a recombinant E1-deleted, partially E3-deleted Ad with Epstein Barr virus glycoprotein gp340/220 inserted into the E1 deletion site under the control of a homologous Ad promoter. In marmosets (tamarins) after three high dose ($5X10^9$ pfu, $1X10^{10}$ pfu and $2X10^{10}$ pfu), intramuscular immunizations and viral challenge, full protection was obtained.

For certain highly infectious diseases, there is a demand for an effective vaccine. Desirably, a vaccine should be effective at a low dosage to control the occurrence of side effects or to enable sufficient amounts of vaccine to be introduced into the animal or human.

There exists a need in the gene therapy art for the development of additional adenovirus vector constructs that do not stimulate immediate immune responses which quickly eliminate the recombinant virus and the therapeutic transgene from the patient. There also exists a need in the vaccine art for new vaccine carriers, which are safe and effective in humans and other mammals.

Summary of the Invention

The present invention meets the need in the art by providing adenovirus nucleotide sequences of chimpanzee origin, a variety of novel vectors, and cell lines expressing chimpanzee adenovirus genes.

In one aspect the invention provides the nucleotide sequence of a chimpanzee C1 adenovirus. See SEQ ID NO: 1.

In another aspect the invention provides the nucleotide sequence of a chimpanzee C68 adenovirus. See SEQ ID NO: 2.

In a further aspect, the invention provides a recombinant adenovirus comprising the DNA sequence of a chimpanzee adenovirus and a selected heterologous gene operatively linked to regulatory sequences directing its expression. The recombinant virus is capable of infecting a mammalian, preferably a human, cell and capable of expressing the heterologous transgene product in the cell. In this vector, the native chimpanzee E1 gene, and/or E3 gene, and/or E4 gene may be deleted. A heterologous gene may be inserted into any of these sites of gene deletion. The heterologous transgene may encode a normal or therapeutic gene which, upon expression, replaces or modifies an inherited or acquired genetic defect. The heterologous gene may be an antigen against which a primed immune response is desired (i.e., a vaccine).

In another aspect, the invention provides a mammalian cell infected with the viral vector described above.

In still a further aspect of this invention, a novel mammalian cell line is provided which expresses a chimpanzee adenovirus gene or functional fragment thereof.

In still a further aspect, the invention provides a method for delivering a transgene into a mammalian cell comprising the step of introducing into the cell an effective amount of a recombinant virus described above.

Another aspect of this invention is a method for delivering to a mammalian patient having a disorder related to an inherited or acquired genetic defect a desired transgene. The method comprises the step of administering to the patient by an appropriate route an effective amount of an above-described recombinant

chimpanzee adenovirus containing a normal or therapeutic transgene, wherein the transgene product is expressed *in vivo*.

Still another aspect of this invention provides a method for eliciting an immune response in a mammalian host to protect against an infective agent. The method comprises the step of administering to the host an effective amount of a recombinant chimpanzee adenovirus comprising a heterologous gene that encodes an antigen from the infecting organism against which the immune response is targeted.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

Brief Description of the Drawings

Fig. 1A is a diagrammatic bar graph illustrating the structure of the chimpanzee adenovirus C1 (also referred to as C-1) and the location of the adenovirus genes thereon by nucleotide position and by map unit numbers appearing under the bar graph. The locations of the late genes (L-1 through L-5) are represented by arrows below the graph with molecular weight indications above the arrows and nucleotide positions below the arrows. The location of the E2a region early TATA box and transcriptional start site was not determined. The E2a region is estimated to begin approximately at nucleotide 27,100. The position of the translation initiation codon for the E2a encoded DNA binding protein is indicated by an asterisk.

Fig. 1B is a line graph showing the correlation between map units and nucleotide (base) pairs of the sequence of C1 [SEQ ID NO: 1].

Fig. 1C is a bar graph illustrating the various Bam HI clones obtained for the C1 Ad, indicating nucleotide numbers, fragment size in nucleotides, clone numbers, and fragment boundaries in nucleotides.

Fig. 2 is a tabular comparison of C1 and C68 predicted amino acid sequences examined for homology to previously described adenoviral protein sequences, Ad4, Ad5, Ad7, Ad12, and Ad40. Symbol "a" indicates that comparison of fragments of different size resulted in an underestimate of homology. Symbol "b" indicates a 95% identity from Ad-4 aa 1-95. A possible mistake in sequence apparently resulted in a frameshift and premature termination in this comparison. Symbol "c" indicates that Ad-5 has 2 small ORF's in this region encoding proteins of 64 and 67 residues with approximately 50% amino acid identity with, respectively, the amino and carboxy halfs of the chimp Ad homologs. Symbol "d" indicates that Ad-3 and Ad-7 fragments were not sequenced for this protein. Symbol "e" indicates that Ad-35 and Ad-4 were not sequenced for this protein. Symbol "f" indicates that the reported sequence for Ad-7 pVIII is 197aa, and the homology begins at aa30 of the chimp Ad sequences. The homology between the chimp Ad's and Ad-7 for the 197 aa region is 98% for C-1 and 90% for C-68.

Fig. 3A is a diagrammatic bar graph illustrating the structure of the chimpanzee adenovirus C68 and the location of the adenovirus genes thereon by nucleotide position and by map unit numbers appearing under the bar graph. The locations of the late genes are represented as described for Fig. 1A. The location of the E2a region early TATA box and transcriptional start site was not determined. The E2a region is estimated to begin approximately at nucleotide 26,800. The position of the translation initiation codon for the E2a encoded

DNA binding protein is indicated by an asterisk. Although the entire genome of C68 has been cloned, certain of the fragments in Fig. 3 have been individually cloned (white bars) or not cloned (shaded bars).

Fig. 3B is a line graph showing the correlation between map units and nucleotide (base) pairs of the sequence of C68 [SEQ ID NO: 2]. White and shaded boxes are defined as in Fig. 3A.

Fig. 3C is a bar graph illustrating the various Pst fragments obtained for the C68 Ad, indicating nucleotide numbers, fragment sizes in nucleotides, clone numbers and fragment boundaries in nucleotides. White and shaded boxes are defined as in Fig. 3A.

Fig. 3D is a bar diagram illustrating Bam HI fragments of the C68 genome indicating nucleotide numbers, fragment size in nucleotides, clone numbers, and fragment boundaries in nucleotides. White and shaded boxes are defined as in Fig. 3A.

Fig. 3E is a bar diagram illustrating the HindIII-B fragment and its nucleotide boundaries and size. White and shaded boxes are defined as in Fig. 3A.

Fig. 4A is a more detailed schematic drawing of pC68-CMV-LacZ.

Fig. 4B is a schematic representation of pBS-Notx2.

Fig. 5A is a schematic drawing of plasmid pGPGK. The arrow indicates the direction of the murine PGK promoter. Restriction sites and marker genes are conventionally labeled.

Fig. 5B is a schematic drawing of plasmid pNEB-C68BamE. This plasmid contains fragments of the LacZ gene (small arrow) flanking either side of the bar indicating the C68 Ad BamE fragment. The large arrow illustrates the Amp^R gene. Restriction sites and marker genes are conventionally labeled.

Fig. 5C is a schematic drawing of plasmid pGPGK-C68BamE in which the BamE fragment from pNEB-C68BamE has been cloned downstream from the PGK promoter of pGPGK.

Fig. 5D is a representation of the PCR amplification of the C68 sequence from pNEB-C68BamE, illustrating the use of primers to introduce a KpnI site just upstream of the C68 E1 region translation initiation codon at nucleotide 576 of the C68 genomic DNA and reduce the sequence distance between the promoter and C68 coding sequence. Location of the primers is indicated.

Fig. 5E is a schematic drawing of plasmid pGPGK-C68E1-ATG, in which the ATG translational start codon was moved closer to the PGK promoter.

Fig. 5F is a schematic drawing of plasmid pBS-C68BamF, in which the BamF fragment was cloned into the BamHI site of pGPGK-C68E1-ATG to generate pGPGK-C68E1 (Fig. 5G).

Fig. 5G is a schematic drawing of plasmid pGPGK-C68E1, containing the complete chimpanzee C68 Ad E1 region under the control of the murine PGK promoter.

Fig. 6A is a schematic drawing of plasmid pGPGK, a duplication of Fig. 5A for purposes of explaining construction of the C1 Ad E1 expression plasmid.

Fig. 6B illustrates the isolation of the 5' end of the C1 E1 region as a 1.9kb SnaBI - XbaI fragment.

Fig. 6C illustrates the use of primers to introduce by PCR amplification a KpnI site just upstream of the C1 E1 region translation initiation codon E1-ATG at nucleotide 577 of the C1 genomic DNA.

Fig. 6D is a schematic drawing of plasmid pGPGK-C1 mu1.3-6.6 (7.4kb).

Fig. 6E is a schematic drawing of plasmid pGPGK-C1-E1ATG.

Fig. 6F is a schematic drawing of plasmid pBS-C1BamI.

Fig. 6G is a schematic drawing of plasmid pGPGK-C1E1, containing the complete chimpanzee C1 Ad E1 region under the control of the murine PGK promoter.

Fig. 7A is a schematic drawing of plasmid pSP72-Pac with indicated restriction endonuclease enzyme cleavage sites.

Fig. 7B is a schematic drawing of plasmid pNEB-C1-BamG.

Fig. 7C is a schematic drawing of plasmid pSP-C1-mu0-1.3.

Fig. 7D is a schematic drawing of plasmid pCMV-ß.

Fig. 7E is a schematic drawing of plasmid pSP-C1-mu0-1.3-CMV-ß.

Fig. 7F is a schematic drawing of plasmid pGEM-3Z.

Fig. 7G is a schematic drawing of plasmid pBS-C1-BamI.

Fig. 7H is a schematic drawing of plasmid pGEM-C1-mu9-10.

Fig. 7I is a schematic drawing of plasmid pBS-C1-BamE.

Fig. 7J is a schematic drawing of plasmid pGEM-C1-mu9-17.

Fig. 7K is a schematic drawing of plasmid pC1-CMV-LacZ, illustrating C1 Ad mu 0 to 1.3, followed by the CMV promoter, a splice donor/splice acceptor sequence (SD/SA), the LacZ gene, a SV40 poly A sequence and C1 Ad mu 9-17, and additional plasmid sequence. The plasmid also contains an ori and Amp^R sequence.

Fig. 8A is a schematic drawing of pSP72-Pac with indicated restriction endonuclease enzyme cleavage sites.

Fig. 8B is a schematic drawing of pNEB-C68-BamE.

Fig. 8C is a schematic drawing of pSP-C68-mu 0-1.3.

Fig. 8D is a schematic drawing of pCMV-ß.

Fig. 8E is a schematic drawing of pSP-C68-mu 0-1.3-CMV-ß.

Fig. 8F is a schematic drawing of pGEM-3Z.

Fig. 8G is a schematic drawing of pBS-C68-BamF.

Fig. 8H is a schematic drawing of pGEM-C68-mu9-10.

Fig. 8I is a schematic drawing of pBS-C68-BamB.

Fig. 8J is a schematic drawing of pGEM-C68-mu9-16.7.

Fig. 8K is a schematic drawing of pC68-CMV-LacZ, illustrating C68 Ad mu 0 to 1.3, followed by the CMV promoter, an SD/SA, the LacZ gene, a SV40 poly A sequence and C68 Ad mu 9-16.7, and additional plasmid sequence. The plasmid also contains an ori and an Amp^R sequence.

Fig. 9A is a schematic drawing of pEGFP-1 (Clontech, Palo Alto, CA).

Fig. 9B is a schematic drawing of a Not-I synthetic linker (New England Biolabs).

Fig. 9C is a schematic drawing of pEGFP-Notx2.

Fig. 9D is a schematic drawing of pC1-CMV-LacZ (from Fig. 7K).

Fig. 9E is a schematic drawing of pC68-CMV-LacZ (from Fig. 8K).

Fig. 9F is a schematic drawing of pC1-CMV-GFP, in which the GFP coding region replaces the LacZ gene of pC1-CMV-LacZ.

Fig. 9G is a schematic drawing of pC68-CMV-GFP, in which the GFP coding region replaces the LacZ gene of pC68-CMV-LacZ.

Fig. 10A is a schematic drawing of pC68-CMV-GFP as discussed in Fig. 9G.

Fig. 10B is a schematic drawing of the C68 genome.

Fig. 10C is a schematic drawing of the C68-SspI-A fragment, which is 35,199 nucleotides.

Fig. 10D is a schematic drawing of the C68-CMV-GFP genome, which is formed by homologous recombination between the C68 mu 9-16.7 sequence in pC68-CMV-GFP and the homologous sequence in the C68-SspI-A fragment.

Fig. 11A is a schematic drawing of pNEB-C1-BamG.

Fig. 11B is a schematic drawing of the C1 genome.

Fig. 11C is a schematic drawing of pNEB-C1-AscI-B.

Fig. 11D is a schematic drawing of a Not-I synthetic linker (New England Biolabs).

Fig. 11E is a schematic drawing of pNEB-C1-AscI-B-NotI.

Fig. 11F is a schematic drawing of the C1 genome.

Fig. 11G is a schematic drawing of the AscI-A fragment of the C1 genome.

Fig. 11H is a schematic drawing of the C1 genome engineered to have a unique NotI site replacing the Spe-I site in the E1B 21K protein coding region.

Detailed Description of the Invention

The present invention provides novel adenovirus vectors and packaging cell lines to produce those vectors for use in the *in vitro* production of recombinant proteins or fragments or other reagents, and for use in the treatment of inherited or acquired genetic disorders and abnormalities in humans and other mammals. The

present invention also provides novel vaccine compositions which comprise those vectors, the vectors comprising an inserted heterologous gene encoding an antigen from an infectious agent.

The methods of the invention involve delivering one or more selected heterologous gene(s) to a mammalian patient by administering a vector of the invention. Because the various vector constructs are derived from chimpanzee rather than from human adenoviruses, the immune system of the patient is not primed to respond immediately to the vector as a foreign antigen. A similar response would be expected where the patient was any mammal other than chimpanzee.

Use of the compositions of this invention thus permits a more stable expression of the selected transgene when administered to a non-chimpanzee, preferably human patient. Use of the compositions of this invention for vaccination permits presentation of a selected antigen for the elicitation of protective immune responses. The recombinant chimpanzee adenoviruses of this invention may also be used for producing heterologous gene products *in vitro*.

I. Cloning of Chimpanzee Adenovirus Sequences

Chimpanzee adenovirus, strain Bertha or C1 [ATCC Accession No. VR-20] and chimpanzee adenovirus, strain Pan-9 or CV68 [ATCC Accession No. VR-594] were obtained from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD. For convenience, the virus CV68 is referred to throughout this specification as "C68". The viruses were originally isolated from feces [C1, Rowe et al, Proc. Soc. Exp. Med., 91:260 (1956)] or mesenteric lymph node [C68, Basnight et al, Am. J. Epidemiol., 94:166 (1971)] of infected chimpanzees.

Little is known about these viruses. However, limited restriction and immunological analyses have been published. For example, C1 was shown to be most similar to Subgroup B human adenoviruses, but it was not neutralized by heterologous sera, and no hemagglutination inhibition was observed [Wigand et al, Intervirology, 30:1 (1989)]. Restriction analysis demonstrated that C68 was most similar to human Ad4 serotype (Subgroup E), but only 1 in 16 enzymes tested did not distinguish C68 and Ad4 [Kitchingman, Gene, 20:205 (1982)].

Both chimpanzee adenoviruses grow well in human cells and were propagated in human embryonic kidney 293 cells. As described in detail in Examples 1 and 2 below, genomic DNA was isolated from purified virus stocks and digested with a panel of restriction enzymes and the restriction fragments cloned and sequenced. The genomic nucleotide sequence of C1 adenovirus is set out in SEQ ID NO: 1. The genomic nucleotide sequence of C68 adenovirus is set out in SEQ ID NO: 2.

Preliminary analysis of the sequence homology between C1, C68 and human adenoviruses was in agreement with the previously mentioned immunologic or restriction enzyme analysis. By reference to Figs. 1A-1C and 3A to 3D, it is shown that the putative E1 region of C1 occurs between about nucleotides 480 and about 3958; and of C68 between about nucleotides 480 and about 3956.

Other gene regions of C1 are identified by homology of the C1 sequence of SEQ ID NO: 1 to the known sequences of human adenoviruses Ad3, Ad5 and Ad7. Similarly, other gene regions of C68 are identified by homology of the C68 sequence of SEQ ID NO: 2 to the known sequence of human adenovirus Ad4 and Ad5. The genomic regions encoding early gene functions for E2a, E2b, E3,

E4, as well as the regions of C1 and C68 encoding late adenoviral gene products, are identified in Tables I and II below.

Table I

C1 Chimpanzee Genome

Gene	Nucleotides	Map Units	Size (nucl./mu)
E1A	480-1540	1.4-4.3	1060/3.0
E1B	1566-3958	4.4-11.1	2392/6.7
E2A	23665-22065	66.6-62.1	1600/4.5
E2B	10379-3959	29.2-11.1	6420/18.1
E3	27181-31375	76.5-88.3	4194/11.8
E4	35228-32535	99.2-91.6	2693/7.6
L1	10893-13864	30.7-39.0	2971/8.4
L2	13925-17591	39.2-49.5	3666/10.3
L3	17641-22083	49.7-62.2	4442/12.5
L4	23697-27813	66.7-78.3	4116/11.6
L5	31556-32551	88.8-91.6	995/2.8

Table II

C68 Chimpanzee Genome

Gene	Nucleotides	Map Units	Size (nucl./mu)
E1A	480-1521	1.3-4.2	1041/2.9
E1B	1560-3956	4.3-10.8	2396/6.6
E2A	23370-21787	64.0-59.7	1583/4.3
E2B	10346-3957	28.3-10.8	6389/17.5
E3	26806-31877	73.4-87.3	5071/13.9
E4	36193-33486	99.1-91.7	2707/7.4
L1	10823-13817	29.6-37.8	2994/8.2
L2	13884-17431	38.0-47.7	3547/9.7
L3	17480-21804	47.9-59.7	4324/11.8
L4	23399-27439	64.1-75.1	4040/11.1
L5	32134-33502	88.0-91.7	1368/3.7

Our preliminary experiments demonstrated that human antisera do not neutralize the chimpanzee adenoviruses in neutralizing antibody assays (see, e.g., International patent application PCT95/03035), thus indicating the desirability of vectors prepared from these sequences for gene therapy in humans. As further described in the examples, plasmids establishing chimpanzee adenovirus E1-expressing cell lines and

recombinant E1-deleted adenoviruses expressing a transgene are prepared.

The viral sequences used in the vectors and cell lines described below may be generated by using the teachings and references contained herein, coupled with standard recombinant molecular cloning techniques known and practiced by those skilled in the art.

II. E1-Expressing Complementation Cell Lines

To generate recombinant chimpanzee adenoviruses (Ad) deleted in any of the genes described above, the function of the deleted gene region, if essential to the replication and infectivity of the virus, must be supplied to the recombinant virus by a helper virus or cell line, i.e., a complementation or packaging cell line. For example, to generate a replication-defective chimpanzee adenovirus vector, a cell line is needed which expresses the E1 gene products of the chimpanzee adenovirus. The protocol for the generation of the cell lines expressing the chimpanzee E1 gene products (Examples 3 and 4) is followed to generate a cell line which expresses any selected chimpanzee adenovirus gene.

Conventional assays were not useful in identifying the chimpanzee adenovirus E1-expressing cell line and a novel AAV augmentation assay was developed to identify the chimpanzee adenovirus E1-expressing cell line. This assay is useful to identify E1 function in cell lines made by using the E1 genes of other uncharacterized adenoviruses, e.g., from other species. That assay is described in Example 4B below.

According to this invention, the selected chimpanzee adenovirus gene, e.g., E1, is under the transcriptional control of a promoter for expression in a selected parent cell line. Inducible or constitutive promoters may be employed for this purpose. Among

inducible promoters are included the sheep metallothionine promoter, inducible by zinc, or the mouse mammary tumor virus (MMTV) promoter, inducible by a glucocorticoid, particularly, dexamethasone. Other inducible promoters, such as those identified in International patent application WO95/13392, published May 18, 1995, and incorporated by reference herein may also be used in the production of packaging cell lines according to this invention. Constitutive promoters in control of the expression of the chimpanzee adenovirus gene may be employed also. The promoter used to express E1 as exemplified below is the well-known constitutive murine PGK promoter.

A parent cell is selected for the generation of a novel cell line expressing any desired C1 or C68 gene. Without limitation, such a parent cell line may be HeLa [ATCC Accession No. CCL 2], A549 [ATCC Accession No. CCL 185], KB [CCL 17], Detroit [e.g., Detroit 510, CCL 72] and WI-38 [CCL 75] cells. These cell lines are all available from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD, USA. Other suitable parent cell lines may be obtained from other sources.

The present invention provides an exemplary cell line which contains and expresses the chimpanzee C68 or C1 Ad E1 gene, as described in detail in Examples 3 and 4 below. Briefly described, the entire chimpanzee adenovirus E1 region was cloned and, by a series of plasmid manipulations, it was placed under the control of a murine PGK promoter in a desired shuttle vector. See Figs. 5A-5G and 6A-6G.

After the desired shuttle vector containing the adenoviral sequences (i.e., pGPGK-C68 E1 described in Example 3) was transfected into the selected parental cell line (e.g., HeLa), expression of the E1

gene was detected. Conventional G418 selection as described in Example 4A was used to generate stable clones of these E1-expressing cells. The resulting cell line is thus able to provide chimpanzee Ad E1 gene products to the replication-defective recombinant virus (see Example 5) to allow productive infection and recovery of the recombinant virus.

The E1-expressing cell lines are useful in the generation of recombinant chimpanzee adenovirus E1 deleted vectors. Cell lines constructed using essentially the same procedures that express one or more other chimpanzee adenoviral gene products are useful in the generation of recombinant chimpanzee adenovirus vectors deleted in the genes that encode those products.

Further, cell lines which express other human Ad E1 gene products are also useful in generating the chimpanzee recombinant Ads of this invention.

III. Recombinant Viral Particles as Vectors

The compositions of this invention comprise desirable viral vectors, that deliver a functional, normal or therapeutic gene to cells. Such vectors comprise chimpanzee adenovirus DNA sequence and a selected heterologous gene operatively linked to regulatory sequences which direct expression of the gene. The vector is capable of expressing the gene product in an infected mammalian cell. The vector is preferably functionally deleted in one or more viral genes. A minigene comprises the heterologous gene under the control of regulatory sequences. Optional helper viruses and/or packaging cell lines supply to the chimpanzee viral vectors any necessary products of deleted adenoviral genes.

The term "functionally deleted" means that a sufficient amount of the gene region is removed or otherwise damaged, e.g., by mutation or modification, so

that the gene region is no longer capable of producing functional products of gene expression. If desired, the entire gene region may be removed.

The viral sequences, helper viruses, if needed, and recombinant viral particles, and other vector components and sequences employed in the construction of the vectors described herein are obtained as described above. The DNA sequences of the two chimpanzee adenoviruses are employed to construct vectors and cell lines useful in the preparation of such vectors.

Modifications of the nucleic acid sequences forming the vectors of this invention, including sequence deletions, insertions, and other mutations may be generated using standard molecular biological techniques and are within the scope of this invention.

A. The "Minigene"

The methods employed for the selection of the transgene, the cloning and construction of the "minigene" and its insertion into the viral vector are within the skill in the art given the teachings provided herein. By "minigene" is meant the combination of a selected heterologous gene and the other regulatory elements necessary to transcribe the gene and express the gene product in a host cell. The gene is operatively linked to regulatory components in a manner which permits its transcription. Such components include conventional regulatory elements necessary to drive expression of the transgene in a cell transfected with the viral vector. Thus the minigene also contains a selected promoter which is linked to the transgene and located, with other regulatory elements, within the selected viral sequences of the recombinant vector.

Selection of the promoter is a routine matter and is not a limitation of this invention.

Useful promoters may be constitutive promoters or regulated (inducible) promoters, which will enable control of the amount of the transgene to be expressed. For example, a desirable promoter is that of the cytomegalovirus immediate early promoter/enhancer [see, e.g., Boshart et al, Cell, 41:521-530 (1985)]. Another desirable promoter includes the Rous sarcoma virus LTR promoter/enhancer. Still another promoter/enhancer sequence is the chicken cytoplasmic ß-actin promoter [T. A. Kost et al, Nucl. Acids Res., 11(23):8287 (1983)]. Other suitable or desirable promoters may be selected by one of skill in the art.

The minigene may also desirably contain nucleic acid sequences heterologous to the viral vector sequences including sequences providing signals required for efficient polyadenylation of the transcript (poly-A or pA) and introns with functional splice donor and acceptor sites. A common poly-A sequence which is employed in the exemplary vectors of this invention is that derived from the papovavirus SV-40. The poly-A sequence generally is inserted in the minigene following the transgene sequences and before the viral vector sequences. A common intron sequence is also derived from SV-40, and is referred to as the SV-40 T intron sequence. A minigene of the present invention may also contain such an intron, desirably located between the promoter/enhancer sequence and the transgene. Selection of these and other common vector elements are conventional [see, e.g., Sambrook et al, "Molecular Cloning. A Laboratory Manual.", 2d edit., Cold Spring Harbor Laboratory, New York (1989) and references cited therein] and many such sequences are available from commercial and industrial sources as well as from Genbank.

As above stated, the minigene is located in the site of any selected deletion in the viral

vector, such as the site of the E1 gene region deletion or E3 gene region deletion, among others which may be selected.

B. Construction of The Viral Plasmid Vector

The chimpanzee adenovirus vectors useful in this invention include recombinant, defective adenoviruses, that is, chimpanzee adenovirus sequences functionally deleted in the E1a or E1b genes, and optionally bearing other mutations, e.g., temperature-sensitive mutations or deletions in other genes. It is anticipated that these chimpanzee sequences are also useful in forming hybrid vectors from other adenovirus and/or adeno-associated virus sequences. Homologous adenovirus vectors prepared from human adenoviruses are described in the published literature [see, for example, Kozarsky I and II, cited above, and references cited therein, U. S. Patent No. 5,240,846].

In the construction of useful chimpanzee adenovirus vectors for delivery of a gene to the human (or other mammalian) cell, a range of adenovirus nucleic acid sequences can be employed in the vectors. A vector comprising minimal chimpanzee adenovirus sequences may be used in conjunction with a helper virus to produce an infectious recombinant virus particle. The helper virus provides essential gene products required for viral infectivity and propagation of the minimal chimpanzee adenoviral vector. When only one or more selected deletions of chimpanzee adenovirus genes are made in an otherwise functional viral vector, the deleted gene products can be supplied in the viral vector production process by propagating the virus in a selected packaging cell line that provides the deleted gene functions in trans.

1. Recombinant Minimal Adenovirus

A minimal chimpanzee Ad virus is a viral particle containing only the adenovirus cis-elements necessary for replication and virion encapsidation, which cis-elements flank the heterologous gene. That is, the vector contains only the cis-acting 5' and 3' inverted terminal repeat (ITR) sequences of the adenoviruses of this invention (which function as origins of replication) and the native 5' packaging/enhancer domains (that contain sequences necessary for packaging linear Ad genomes and enhancer elements for the E1 promoter). See, for example, the techniques described for preparation of a "minimal" human Ad vector in International Patent Application WO96/13597, published May 9, 1996, and incorporated herein by reference.

2. Other Defective Adenoviruses

Recombinant, replication-deficient adenoviruses of this invention may also contain more than the minimal chimpanzee adenovirus sequences defined above. These other Ad vectors can be characterized by deletions of various portions of gene regions of the virus, and infectious virus particles formed by the optional use of helper viruses and/or packaging cell lines, as described herein.

As one example, suitable vectors may be formed by deleting all or a sufficient portion of the adenoviral immediate early gene E1a and delayed early gene E1b, so as to eliminate their normal biological functions. Replication-defective E1-deleted viruses are capable of replicating and producing infectious virus when grown on a chimpanzee adenovirus-transformed, complementation cell line containing functional adenovirus E1a and E1b genes which provide the corresponding gene products in trans. Based on the homologies to known adenovirus sequences, it is

anticipated that, as is true for the human recombinant E1-deleted adenoviruses of the art, the resulting recombinant chimpanzee adenovirus is capable of infecting many cell types and can express a transgene, but cannot replicate in most cells that do not carry the chimpanzee E1 region DNA unless the cell is infected at a very high multiplicity of infection.

As another example, all or a portion of the adenovirus delayed early gene E3 may be eliminated from the chimpanzee adenovirus sequence which forms a part of the recombinant virus. The function of chimpanzee E3 is believed to be irrelevant to the function and production of the recombinant virus particle.

Chimpanzee adenovirus vectors may also be constructed having a deletion of the E4 gene. Still another vector of this invention contains a deletion in the delayed early gene E2a.

Deletions may also be made in any of the late genes L1 through L5 of the chimpanzee adenovirus genome. Similarly, deletions in the intermediate genes IX and IVa_2 may be useful for some purposes. Other deletions may be made in the other structural or non-structural adenovirus genes.

The above discussed deletions may be used individually, i.e., an adenovirus sequence for use in the present invention may contain deletions of E1 only. Alternatively, deletions of entire genes or portions thereof effective to destroy their biological activity may be used in any combination. For example, in one exemplary vector, the adenovirus sequence may have deletions of the E1 genes and the E4 gene, or of the E1, E2a and E3 genes, or of the E1 and E3 genes, or of E1, E2a and E4 genes, with or without deletion of E3, and so on. As discussed above, such deletions may be used in

combination with other mutations, such as temperature-sensitive mutations, to achieve a desired result.

The minigene containing the transgene may be inserted optionally into any deleted region of the chimpanzee Ad virus. Alternatively, the minigene may be inserted into an existing gene region to disrupt the function of that region, if desired.

The construction of exemplary E1-deleted chimpanzee Ad virus vectors is described in detail in Example 5 below. Desirably, such a vector contains chimpanzee adenovirus sequences Ad m.u. 0-1.3, followed by a minigene containing the transgene of interest (e.g., a therapeutic gene for the correction of a genetic defect in a patient or a marker gene to visualize infected cells) and the sequence Ad m.u. 9 to 100 of C1 or C68. These recombinant adenoviruses are functionally deleted of E1a and E1b.

C. Production of the Recombinant Viral Particle

1. Helper Viruses

Depending upon the chimpanzee adenovirus gene content of the viral vectors employed to carry the minigene, a helper adenovirus or non-replicating virus fragment may be necessary to provide sufficient chimpanzee adenovirus gene sequences necessary to produce an infective recombinant viral particle containing the minigene.

Useful helper viruses contain selected adenovirus gene sequences not present in the adenovirus vector construct and/or not expressed by the packaging cell line in which the vector is transfected. A preferred helper virus is desirably replication-defective and contains a variety of adenovirus genes in addition to the sequences described above. The helper

virus is desirably used in combination with the E1-expressing cell lines described herein.

Most preferably for C68, the "helper" virus is a fragment formed by clipping the C terminal end of the C68 genome with SspI, which removes about 1300 bp from the left end of the virus. This clipped virus is then co-transfected into the E1-expressing cell line with the plasmid DNA, thereby forming the recombinant virus by homologous recombination with the C68 sequences in the plasmid.

Because there is no similarly unique restriction site in the 5' end of C1, to create a recombinant virus, the SpeI site at position 1733 is replaced with a unique Not I site, generating the modified C1 NotI genome of about 35,526 bp. See, e.g., Figs 12A-12F.

Helper viruses may also be formed into poly-cation conjugates as described in Wu et al, J. Biol. Chem., 264:16985-16987 (1989); K. J. Fisher and J. M. Wilson, Biochem. J., 299:49 (April 1, 1994). Helper virus may optionally contain a second reporter minigene. A number of such reporter genes are known to the art. The presence of a reporter gene on the helper virus which is different from the transgene on the adenovirus vector allows both the Ad vector and the helper virus to be independently monitored. This second reporter is used to enable separation between the resulting recombinant virus and the helper virus upon purification.

2. Assembly of Viral Particle and Infection of a Cell Line

Assembly of the selected DNA sequences of the adenovirus, and the transgene and other vector elements into various intermediate plasmids and shuttle vectors, and the use of the plasmids and vectors

to produce a recombinant viral particle are all achieved using conventional techniques. Such techniques include conventional cloning techniques of cDNA such as those described in texts [Sambrook et al, cited above], use of overlapping oligonucleotide sequences of the adenovirus genomes, polymerase chain reaction, and any suitable method which provides the desired nucleotide sequence. Standard transfection and co-transfection techniques are employed, e.g., $CaPO_4$ precipitation techniques. Other conventional methods employed include homologous recombination of the viral genomes, plaquing of viruses in agar overlay, methods of measuring signal generation, and the like.

For example, following the construction and assembly of the desired minigene-containing viral vector, the vector is transfected *in vitro* in the presence of a helper virus into the packaging cell line. Homologous recombination occurs between the helper and the vector sequences, which permits the adenovirus-transgene sequences in the vector to be replicated and packaged into virion capsids, resulting in the recombinant viral vector particles. The current method for producing such virus particles is transfection-based. However, the invention is not limited to such methods.

The resulting recombinant chimpanzee adenoviruses are useful in transferring a selected transgene to a selected cell. In *in vivo* experiments with the recombinant virus grown in the packaging cell lines, the E1-deleted recombinant chimpanzee adenovirus demonstrates utility in transferring a transgene to a non-chimpanzee, preferably a human, cell.

IV. Use of the Recombinant Virus Vectors

The resulting recombinant chimpanzee adenovirus containing the minigene (produced by cooperation of the adenovirus vector and helper virus or adenoviral vector and packaging cell line, as described above) thus provides an efficient gene transfer vehicle which can deliver the transgene to a human patient *in vivo* or *ex vivo*.

The above-described recombinant vectors are administered to humans according to published methods for gene therapy. A chimpanzee viral vector bearing the selected transgene may be administered to a patient, preferably suspended in a biologically compatible solution or pharmaceutically acceptable delivery vehicle. A suitable vehicle includes sterile saline. Other aqueous and non-aqueous isotonic sterile injection solutions and aqueous and non-aqueous sterile suspensions known to be pharmaceutically acceptable carriers and well known to those of skill in the art may be employed for this purpose.

The chimpanzee adenoviral vectors are administered in sufficient amounts to transduce the human cells and to provide sufficient levels of gene transfer and expression to provide a therapeutic benefit without undue adverse or with medically acceptable physiological effects, which can be determined by those skilled in the medical arts. Conventional and pharmaceutically acceptable routes of administration include, but are not limited to, direct delivery to the liver, intranasal, intravenous, intramuscular, subcutaneous, intradermal, oral and other parental routes of administration. Routes of administration may be combined, if desired.

Dosages of the viral vector will depend primarily on factors such as the condition being treated, the age, weight and health of the patient, and may thus

vary among patients. For example, a therapeutically effective human dosage of the viral vector is generally in the range of from about 20 to about 100 ml of saline solution containing concentrations of from about 1 x 10^9 to 1 x 10^{11} pfu/ml virus vector. A preferred human dosage is estimated to be about 50 ml saline solution at 2 x 10^{10} pfu/ml. The dosage will be adjusted to balance the therapeutic benefit against any side effects and such dosages may vary depending upon the therapeutic application for which the recombinant vector is employed. The levels of expression of the transgene can be monitored to determine the frequency of dosage administration.

An optional method step involves the co-administration to the patient, either concurrently with, or before or after administration of the viral vector, of a suitable amount of a short acting immune modulator. The selected immune modulator is defined herein as an agent capable of inhibiting the formation of neutralizing antibodies directed against the recombinant vector of this invention or capable of inhibiting cytolytic T lymphocyte (CTL) elimination of the vector. The immune modulator may interfere with the interactions between the T helper subsets (T_{H1} or T_{H2}) and B cells to inhibit neutralizing antibody formation. Alternatively, the immune modulator may inhibit the interaction between T_{H1} cells and CTLs to reduce the occurrence of CTL elimination of the vector.

A variety of useful immune modulators and dosages for use of same are disclosed, for example, in Yang *et al.*, J. Virol., 70(9) (Sept., 1996); International Patent Application No. WO96/12406, published May 2, 1996; and International Patent Application No.PCT/US96/03035, all incorporated herein by reference.

The recombinant chimpanzee adenoviruses may also be employed as vaccines or immune response-inducing compositions. The present invention provides a recombinant replication-defective chimpanzee Ad which can contain in any of its adenovirus sequence deletions a gene encoding a desired antigen. The chimpanzee adenovirus is likely to be better suited for use as a live recombinant virus vaccine in different animal species compared to an adenovirus of human origin. The recombinant adenoviruses can be used as prophylactic or therapeutic vaccines against any pathogen for which the antigen(s) crucial for induction of an immune response and able to limit the spread of the pathogen has been identified and for which the cDNA is available.

Because the recombinant chimpanzee adenoviruses described above are deleted in the E1 sequences, the adenoviruses are replication defective and thus highly unlikely to spread within a host or among individuals. The recombinant virus lacks oncogenic potential because the E1 gene, that can function as an oncogene in some adenovirus strains, has been deleted.

With respect to efficacy, the recombinant, replication-defective adenoviruses of this invention are expected to be highly efficacious at inducing cytolytic T cells and antibodies to the inserted heterologous antigenic protein expressed by the virus. This has been demonstrated with a recombinant, replication-defective human Ad containing a sequence encoding the rabies virus glycoprotein as the heterologous gene. See, e.g., Z. Q. Xiang *et al.*, Virol., 219:220-227 (1996).

As described above and in the examples below, in the site of the E1 deletion of either of the two chimpanzee adenoviruses of this invention, and under control of a promoter heterologous to adenovirus, a sequence encoding a protein heterologous to the

adenovirus is inserted using techniques known to those of skill in the art. The heterologous nucleic acid encodes a protein which is desirably capable of inducing an immune response to a pathogen when administered to an immunocompetent host. Such a protein may be a protein from, among others, rabies virus, human papilloma virus, human immunodeficiency virus (HIV), and respiratory syncytial virus (RSV), as well as antigens associated with diseases of other mammals.

It is also anticipated that the vaccine method of the present invention may be employed with a tumor-associated protein specific for a selected malignancy. These tumor antigens include viral oncogenes, such as E6 and E7 of human papilloma virus, or cellular oncogenes such as mutated ras or p53. Particularly, where the condition is human immunodeficiency virus (HIV) infection, the protein is preferably HIV glycoprotein 120 for which sequences are available from GenBank. Where the condition is human papilloma virus infection, the protein is selected from the group consisting of E6, E7 and/or L1 [Seedorf, K. et al, Virol., 145:181-185 (1985)]. Where the condition is respiratory syncytial virus infection, the protein is selected from the group consisting of the glyco- (G) protein and the fusion (F) protein, for which sequences are available from GenBank. In addition to these proteins, other virus-associated proteins, including proteins which are antigens for disease-causing agents of other mammals, e.g., domestic animals, horses, farm animals, etc., are readily available to those of skill in the art. Selection of the heterologous proteins is not a limiting factor in the design of vaccine compositions of this invention.

A recombinant replication-defective chimpanzee adenoviral vector bearing a gene encoding an immunogenic protein may be administered to a human or other mammalian patient, preferably suspended in a biologically compatible solution or pharmaceutically acceptable delivery vehicle. A suitable vehicle is sterile saline. Other aqueous and non-aqueous isotonic sterile injection solutions and aqueous and non-aqueous sterile suspensions known to be pharmaceutically acceptable carriers and well known to those of skill in the art may be employed for this purpose.

Optionally, a vaccinal composition of the invention may be formulated to contain other components, including, e.g. adjuvants, stabilizers, pH adjusters, preservatives and the like. Such components are well known to those of skill in the vaccine art.

The recombinant, replication defective adenoviruses are administered in a "pharmaceutically effective amount", that is, an amount of recombinant adenovirus that is effective in a route of administration to transfect the desired cells and provide sufficient levels of expression of the selected gene to provide a vaccinal benefit, i.e., some measurable level of protective immunity.

Conventional and pharmaceutically acceptable routes of administration include, but are not limited to, intranasal, intramuscular, intratracheal, subcutaneous, intradermal, rectal, oral and other parental routes of administration. Routes of administration may be combined, if desired, or adjusted depending upon the immunogen or the disease. For example, in prophylaxis of rabies, the subcutaneous, intratracheal and intranasal routes are preferred. The route of administration primarily will depend on the nature of the disease being treated.

Doses or effective amounts of the recombinant replication-defective Ad virus will depend primarily on factors such as the condition, the selected gene, the age, weight and health of the animal, and may thus vary among animals. For example, a prophylactically effective amount or dose of the Ad vaccine is generally in the range of from about 100 μl to about 10 ml of saline solution containing concentrations of from about 1 x 10^4 to 1 x 10^7 plaque forming units (pfu) virus/ml. A preferred dose is from about 1 to about 10 ml saline solution at the above concentrations. The levels of immunity of the selected gene can be monitored to determine the need, if any, for boosters. Following an assessment of antibody titers in the serum, optional booster immunizations may be desired.

An additional use of the recombinant adenovirus vectors described herein resides in their use as expression vectors for the production of the products encoded by the heterologous genes. For example, the recombinant adenoviruses containing a gene inserted into the location of an E1 deletion may be transfected into an E1-expressing cell line as described above. The transfected cells are then cultured in the conventional manner, allowing the recombinant adenovirus to express the gene product from the promoter. The gene product may then be recovered from the culture medium by known conventional methods of protein isolation and recovery from culture.

The following examples illustrate the cloning of the chimpanzee adenoviruses and the construction and testing of the chimpanzee Ad E1 expressing cell line and the construction of exemplary recombinant adenovirus vectors of the present invention. These examples are illustrative only, and do not limit the scope of the present invention.

Example 1 - Virus Stocks and Propagation

The C1 [ATCC Accession No. VR-20] and C68 [ATCC Accession No. 594] virus stocks were obtained and propagated in 293 cells [ATCC CRL1573] cultured in Dulbecco's Modified Eagles Medium (DMEM; Sigma, St. Louis, MO.) supplemented with 10% fetal calf serum (FCS) [Sigma or Hyclone, Logan, UT] and 1 % Penicillin-Streptomycin (Sigma). Infection of 293 cells was carried out in DMEM supplemented with 2% FCS for the first 24 hours, after which FCS was added to bring the final concentration to 10%. Infected cells were harvested when 100% of the cells exhibited virus-induced cytopathic effect (CPE), collected, and concentrated by centrifugation. Cell pellets were resuspended in 10 mM Tris (pH 8.0), and lysed by 3 cycles of freezing and thawing.

Virus preparations were obtained following two ultra centrifugation steps on cesium chloride density gradients and stocks of virus were diluted to 1 x 10^{12} particles/ml in 10 mM Tris/100 mM NaCl/50% glycerol and stored at -70°C.

Example 2 - Cloning and Sequencing of Viral Genomic DNA

Genomic DNA was isolated from the purified virus preparations of Example 1, following standard methods [see, e.g., M. S. Horwitz et al, "Adenoviridae and Their Replication", Virology, second edition, pp. 1712, ed. B. N. Fields et al, Raven Press Ltd., New York (1990); B. J. Carter, in "Handbook of Parvoviruses", ed. P. Tijsser, CRC Press, pp. 155-168 (1990)] and digested with a panel of 16 restriction enzymes following the manufacturers' recommendations. Enzymes that cut the DNA 10-15 times were utilized for cloning of the viral DNA into pBluescript SK+. Except as noted, all restriction

and modifying enzymes used in this and the following examples were obtained from Boehringer Mannheim, Indianapolis, IN.

Manipulation of the genomic DNA to remove the covalently attached terminal protein was performed [Berkner and Sharp, Nucleic Acids Res., 11: 6003 (1983)]. Taking advantage of the absence of Pac-I restriction sites, synthetic PacI linkers (New England Biolabs, Beverly, MA) were ligated onto the ends of the genomic DNA. Genomic DNA was digested with BamHI, PstI, SalI or XbaI and the restriction fragments (all but the genomic terminal fragments) were cloned into pBluescript SK+ (Stratagene, La Jolla, CA). Fragments containing the left and right genomic termini were cloned into pNEB-193 (New England Biolabs, Beverly, MA) as Pac-I/BamHI or Pac-I/Pst-I fragments.

The clones generated for C1 and C68 are illustrated in Figs. 1C and 3C, respectively. The cloned fragments are described in Table III(C1) [nucleotide sequence numbers correspond with SEQ ID NO: 1] and Table IVA-IVB (C68) [nucleotide sequence numbers correspond with SEQ ID NO: 2].

Table III

Construct Name	Insert Size	Clone #	Sequence
pBS:C1-Bam-A	8477	250,260 281	6135-14611
pBS:C1-Bam-B	8253	285	24678-32930
pBS:C1-Bam-C	3990	252	17259-21248
pBS:C1-Bam-D	3429	263,269 275	21250-24677
pBS:C1-Bam-E	2537	251	3598- 6134
pBS:C1-Bam-F	2203	267,270, 279	14612-16814
pNEB:C1-Bam-G	1927	516	1-1927 left end
pBS:C1-Bam-H	1632	486,487	32931-34562
pBS:C1-Bam-I	1538	288-293 483,485	2060- 3597
pNEB:C1-Bam-J	962	519	34563-35524 right end
pBS:C1-Bam-K	288	256,295 296,,298	16971-17258
pBS:C1-Bam-L	156	260	16815-16970
pBS:C1-Bam-M	132	259,261 262	1928- 2059
pBS:C1-Bam-A/Pst		423-428	subclone of 250
pBS:C1-Bam-B/HindIII		429-434	subclone of 285
pNEB:C-1AscB	7937	955	1-7937 left end

Table IVA

Construct Name	Size	Clone #	Sequence
pBS:C68-Pst-A	6768		24790-31554
pBS:C68-Pst-B	6713	133,141 213-217, 303-305	4838-11550
pBS:C68-Pst-C	5228	219-221	14811-20038
pBS:C68-Pst-D	2739	78,140	12072-14810
pBS:C68-Pst-E	2647	127,129 146,151	20039-22685
pBS:C68-Pst-F	1951	138,149	32046-33996
pNEB:C68-Pst-G	1874	502,505 506	1-1874 left end
pBS:C68-Pst-H	1690	128,135 145,152	23094-24783
pBS:C68-Pst-I	1343	222-224	33997-35339
pNEB:C68-Pst-J	1180	508	35340-36519 right end
pBS:C68-Pst-K	1111	87,131 132,136 225-230	2763-3873
pBS:C68-Pst-L	964	320,321, 323,324	3874-4837
pBS:C68-Pst-M	888	319,322	1875-2762
pBS:C68-Pst-N	408	84,125 130	22686-23093
pBS:C68-Pst-O	380		31666-32045
pBS:C68-Pst-P	285	79,126	11551-11835
pBS:C68-Pst-Q	236		11836-12071
pBS:C68-Pst-R	114	82	31552-31665

Table IVB

BamHI Fragments	Size	Clone #	Sequence
pBS:C68-Bam-A	16684		19836-36519 right end
pBS:C68-Bam-B	8858	95,99 101-103 119-121, 165, 166, 169,171	3582-12439
pBS:C68-Bam-C	4410	104,106 167,179 171	12440-16849
pBS:C68-Bam-D	2986	195-197	16850-19835
pNEB:C68-Bam-E	2041	537,545	1- 2041 left end
pBS:C68-Bam-F	1540	198-200	2042- 3581
HindIII Fragments			
pBR:C-68-Hind-B	9150	489,419, 492	23471-32620

Cloned restriction fragments were ordered in the genome by comparison to known adenoviral sequences. The nucleotide sequence of both viruses was determined [Commonwealth Biotechnologies Incorporated, Richmond, VA]. The nucleotide sequence of the top strand of C1 DNA is reported in SEQ ID NO: 1. The nucleotide sequence of the top strand of C68 DNA is reported in SEQ ID NO: 2. Restriction maps were generated using a number of enzymes and compared to data obtained from restricted genomic DNA following electrophoreses on agarose gels.

Regulatory and coding regions in the viral DNA sequences were identified by homology to known adenoviral sequences using the Mac Vector program (Oxford Molecular Group) and a MacIntosh Quadra 610 computer (Apple Computer, Cupertino, CA). See Tables I and II. Open

reading frames were translated and the predicted amino acid sequences examined for homology to previously described adenoviral protein sequences, Ad4, Ad5, Ad7, Ad12, and Ad40. See Fig. 2 below.

The C1 E1 coding region is defined as the sequences between the E1A translation initiation site at nucleotide 576 of SEQ ID NO: 1 and the E1B translation termination signal at nucleotide 3507 of SEQ ID NO: 1. The corresponding sequences in the C68 genome are located at nucleotides 577 and 3510 of SEQ ID NO: 2. Other open reading frames and regulatory elements of the viruses are being examined for homology with other adenoviral sequences.

Our preliminary experiments have demonstrated that human antisera do not neutralize the chimpanzee adenoviruses in neutralizing antibody assays.

Example 3 - Generation of Plasmid Vectors Expressing the C1 and C68 E1 Genes

Plasmid vectors were constructed which encode the C1 and C68 E1 region genes, and these plasmids were used to generate stable cell lines expressing viral E1 proteins.

A. pGPGK-C68 E1

pGPGK (gift of Gaung Ping Gao, University of Pennsylvania, Philadelphia, PA) is illustrated in Fig. 5A. pGPGK is a 5.5 kb plasmid containing the known murine PGK promoter (indicated by the arrow on Fig. 5A), followed by a multiple cloning site, a growth hormone polyA sequence, an SV40 ori, a neomycin resistance gene, an SV40 polyA sequence and an ampicillin resistance gene. The remainder of the plasmid is additional plasmid sequence.

As shown in Fig. 5B, the 5' end of the C-68 E1 region was derived from clone 245 which contains a defective version of the C-68 BamHI-E fragment (2042 base pairs) in pNEB-193, i.e., clone 245 was shown to lack approximately the first 30 base pairs of the C-68 genomic sequence, a region not included in the final product of this construction scheme, pGPGK-C68 E1. This plasmid pNEB-C68BamE was digested with BamHI and HindIII and the 2.1kb fragment was ligated with similarly digested pGPGK DNA. The resulting plasmid is designated pGPGK-C68 BamE, illustrated in Fig. 5C.

PCR primers SF-34 (GCAGGTACCGCGAGTCAGATCTACAC) [SEQ ID NO: 4] and SF-35 (CTGTCTGAGCTAGAGCTC) [SEQ ID NO: 5] were designed to introduce a KpnI restriction site 31 base pairs upstream of the E1A translation initiation site (nucleotide 577 of SEQ ID NO: 2). Using clone 245 as template, a 293bp PCR product was obtained using reagents from Perkin Elmer (Foster City, CA) under the following conditions: 94 = BOC x 5 minutes; 25 cycles of 94 = BOC x 1 minute; 54 = BOC x 1 minute; 72=BOC x 2 minutes; and a final extension cycle of 72= BOC x 7 minutes. The PCR product was purified and is indicated by the hatched bar in Fig. 5D.

The PCR product was digested with KpnI and NheI, yielding a 253bp fragment, which was purified and ligated with similarly digested pGPGK-C68 BamE (Fig. 5C) DNA to yield pGPGK-C68 E1-ATG (Fig. 5E).

The region derived from the PCR step was sequenced for several isolates and the adenovirus insert in pGPGK-C68E1-ATG was shown to match the expected sequence derived from C-68 genomic DNA. pGPGK-C68 E1-ATG (Fig. 5E) was digested with BamHI and the linearized plasmid treated with calf intestinal phosphatase. The purified/phosphatased backbone was ligated with the

1544bp C-68 BamF fragment isolated from pBS-C68 BamF (Fig. 5F) to yield the final plasmid, designated pGPGK-C68 E1 (Fig. 5G).

The C-68 derived sequence in plasmid pGPGK-C68 E1 ends at the BamHI site corresponding to nucleotide 3581 of SEQ ID NO: 2 in the C-68 genomic sequence, which is 80bp downstream of the end of the E1B coding region. This expression plasmid contains from about nucleotide 546 to nucleotide 3581 of SEQ ID NO: 2 which encodes E1a and E1b of chimpanzee Ad C68 under the control of the PGK promoter.

B. pGPGK-C1 E1

The C1 Ad E1 expression plasmid was constructed in a manner similar to that described above for the C68 E1 expression plasmid. Refer to Figs. 6A through 6G.

The 5' end of the C-1 E1 region is isolated as a 1.9kb SnaBI - XbaI fragment (Fig. 6B) and is cloned into pGPGK (Fig. 6A) digested with XbaI and EcoRV. The resulting pGPGK-C1 (map units 1.3-6.6) (Fig. 6D) is used as the template for PCR. Primers are designed to introduce a KpnI site just upstream of the C1 E1 region translation initiation codon (E1-ATG) at nucleotide 578 of the C1 genomic DNA. (See Fig. 6C).

The PCR product is double digested with KpnI and KspI and ligated with similarly digested pGPGK-C1 (m.u. 1.3-6.6) to yield pGPGK-C1 E1-ATG. Partial digestion of pGPGK-C1 E1-ATG (Fig. 6E) with BamHI and isolation of the full length linear DNA, followed by XbaI digestion and isolation of the full length band, followed by ligation with similarly digested pBS-C1 Bam-I (Fig. 6F) yields the final product, pPGPK-C1 E1 (Fig. 6G). The C-1 derived sequence in plasmid pGPGK-C1 E1 ends at the BamHI site corresponding to nucleotide 3599 in the C-1 genomic sequence, which is 90bp downstream of

the end of the E1B coding region. This expression plasmid contains from about nucleotide 548 to about nucleotide 3581 of SEQ ID NO: 1 which encodes E1a and E1b of Ad C1 under the control of the PGK promoter.

Example 4 - Generation of Cell Lines Expressing Chimpanzee Adenovirus E1 Proteins

Cell lines expressing viral E1 proteins were generated by transfecting HeLa (ATCC Acc. No. CCL2) and A549 (ATCC Acc. No. CCL185) cell lines with either pGPGK-C1 E1 or pGPGK-68 E1 of Example 3. These cell lines are necessary for the production of E1 deleted recombinant chimpanzee adenoviruses by co-transfection of genomic viral DNA and the expression plasmids described above. Transfection of these cell lines, as well as isolation and purification of recombinant chimpanzee adenoviruses therefrom were performed by methods conventional for other adenoviruses, i.e., human adenoviruses [see, e.g., Horwitz, cited above and other standard texts].

A. Cell lines expressing C1 and C68 E1 proteins

HeLa and A549 cells in 10cm dishes were transfected with 10 μg of pGPGK-C1-E1 DNA or pGPGK-C68-E1 DNA using a Cellphect™ kit (Pharmacia, Uppsala, Sweden) and following the manufacturer's protocol. 22 hours post-transfection, the cells were subjected to a three minute glycerol shock (15% glycerol in Hepes Buffered Saline, pH 7.5) washed once in DMEM (HeLa) or F12K (A549; Life Technologies, Inc., Grand Island, NY) media supplemented with 10% FCS, 1% Pen-Strep, then incubated for six hours at 37°C in the above described media. The transfected cells were then split into duplicate 15cm plates at ratios of 1:20, 1:40, 1:80, 1:160, and 1:320. Following incubation at 37°C overnight, the media was

supplemented with G418 (Life Technologies, Inc.) at a concentration of 1μg/ml. The media was replaced every 5 days and clones were isolated 20 days post-transfection.

Thirty-two A549 and 16 HeLa C1 E1 cell clones and 40 A549 and 37 HeLa C68 E1 cell clones were isolated and assayed for their ability to augment adeno-associated virus (AAV) infection and expression of recombinant LacZ protein as described below.

B. AAV Augmentation Assay for Screening E1 Expressing Cell Lines

AAV requires adenovirus-encoded proteins in order to complete its life cycle. The adenoviral E1 proteins as well as the E4 region encoded ORF-6 protein are necessary for the augmentation of AAV infection. A novel assay for E1 expression based on AAV augmentation is disclosed herein. Briefly, the method for identifying adenoviral E1- expressing cells comprises the steps of infecting in separate cultures a putative adenovirus E1-expressing cell and a cell containing no adenovirus sequence, with both an adeno-associated virus (AAV) expressing a marker gene and an AAV expressing the ORF6 of the E4 gene of human adenovirus, for a suitable time. The marker gene activity in the resulting cells is measured and those cells with significantly greater measurable marker activity than the control cells are selected as confirmed E1-expressing cells. In the following experiment, the marker gene is a lacZ gene and the marker activity is the appearance of blue stain.

For example, the cell lines described above, as well as untransfected control cells (A549 and HeLa) are infected with 100 genomes per cell of an AAV vector bearing a marker gene, e.g., AV.LacZ [K. Fisher *et al.*, J. Virol., 70:520 (1996)] and an AAV vector expressing the ORF6 region of human Ad5 (AV.orf6) (see SEQ ID NO: 3). The DNA sequence [SEQ ID NO: 3] of the

plasmid pAV.CMVALP.GRE-ORF6, also called AV.orf6, generates a novel recombinant adeno-associated virus (rAAV) containing the *LacZ* transgene and the Ad E4 ORF 6, which is an open reading frame whose expression product facilitates single-stranded (ss) to double-stranded (ds) conversion of rAAV genomic DNA. In SEQ ID NO: 3, the AAV 5' inverted terminal repeat (ITR) is at nucleotides 53-219; the cytomegalovirus (CMV) enhancer/promoter is at nucleotides 255-848; the human placenta alkaline phosphatase cDNA (ALP) is at nucleotides 914-2892; the SV40 polyadenylation (polyA) signal is at nucleotides 2893-3090; the glucocorticoid dependent (GRE) promoter is at nucleotides 3114-3393; the Ad5 E4-ORF6 cDNA is at nucleotides 3402-4286; the SV40 polyA signal is at nucleotides 4315-4512; and the 3' AAV ITR is at nucleotides 4547 - 4713. All other nucleotides are plasmid-derived. These vectors are incubated in medium containing 2% FCS and 1% Pen-Strep at 37°C for 4 hours, at which point an equal volume of medium containing 10% FCS is added. It should be understood by one of skill in the art that any marker gene (or reporter gene) may be employed in the first AAV vector of this assay, e.g., alkaline phosphatase, luciferase, and others. An antibody-enzyme assay can also be used to quantitate levels of antigen, where the marker expresses an antigen. The assay is not limited by the identity of the marker gene. Twenty to twenty-four hours post-infection, the cells are stained for LacZ activity using standard methods. After 4 hours the cells are observed microscopically and cell lines with significantly more blue cells than the A549 or HeLa cell controls are scored as positive.

Eight A549 (A-2,3,8,13,15,18,23,38) and five HeLa (H-3,4,15,16,20) cell clones are significantly positive in the AAV augmentation assay and the three best

of each cell type (A-18, A-23, A-13 and H-16, H-4, H-20), when tested, support the growth of E1 deleted recombinant C68 viruses.

Four A549 (A-3, 6, 19, 22) and nine HeLa (H-2,5-7, 11-16) cell clones are significantly positive in the AAV augmentation assay and the three best of each cell type (A-3, A-19, A-22 and H-5, H-12, H-14), when tested, support the growth of E1 deleted recombinant C1 viruses.

Example 5 - Generation of Recombinant Chimpanzee Adenoviruses

Recombinant chimpanzee adenovirus vectors are prepared using the C1 and C68 sequences described herein and HEK293 cells. The cell lines described in Example 4 may also be used similarly. Plasmids used to construct C68 and C1 recombinant adenovirus vectors are illustrated in Figs. 7A through 7K, and 8A through 8K, respectively. See also Figs. 11A-11K.

A. pC1-CMV-LacZ

pSP72 (Promega, Madison, WI) is modified by digestion with BglII, followed by filling-in of the ends with Klenow and ligation with a synthetic 12bp PacI linker (New England Biolabs, Beverly, MA) to yield pSP72-Pac (Fig. 7A), which contains a large multiple cloning site with conventional restriction enzyme cleavage sites.

pSP72-Pac is digested with PacI and EcoRV and ligated with the 465bp PacI-SnaBI fragment isolated from pBSC1-BamG (Fig. 7B) to yield pSP-C1-MU 0-1.3 (Fig. 7C). The CMV promoter-driven LacZ gene is isolated from pCMV-ß (Clontech, Palo Alto, CA; Fig. 7D) as a 4.5kb EcoRI/SalI fragment and ligated with similarly digested pSP-C1-MU 0-1.3 DNA to yield pSP-C1-MU 0-1.3-CMV-ß.

For the initial step in the isolation of the C1 Ad map units 9-16 region, pGEM-3Z (Promega, Madison, WI; Fig. 7F) and pBS-C1-BamI (Fig. 7G) are digested with BamHI and SphI and the 310bp fragment from pBS-C1-BamI is ligated with the pGEM-3Z backbone to form pGEM-C1-MU9-10 (Fig. 7H). C1 map units 10-17 are isolated from pBS-C1 BamE (Fig. 7I) by digestion with BamHI. The 2.5 kb fragment is ligated with BamHI-digested pGEM-C1-MU9-10 to form pGEM-C1-MU9-17 (Fig. 7J). The 2.9 kb fragment containing C1 map unit 9-17 region is isolated from pGEM-C1-MU9-17 by digestion with HindIII and ligated with pSP-C1-MU 0-1.3-ß (Fig. 7E) digested with HindIII to form the final plasmid, pC1-CMV-LacZ (Fig. 7K).

pC1-CMV-LacZ (Fig. 7K) thus contains C1 Ad mu 0 to 1.3, followed by the CMV promoter, an SD/SA, the LacZ gene, a SV40 poly A sequence and C1 Ad mu. 9-17, as well as additional plasmid sequence. This plasmid is co-transfected into the E1-expressing cell line with a left terminal clipped C1 Ad fragment (or a replication-defective C1 Ad helper virus) to produce by homologous recombination a recombinant chimpanzee adenovirus carrying the LacZ gene.

C. pC68-CMV-LacZ

pSP72-Pac (Fig. 8A; also Fig. 7A) is digested with PacI and EcoRV and ligated with the 465bp PacI-SnaBI fragment isolated from pBS-C68-BamE (Fig. 8B) to yield pSP-C68-MU 0-1.3 (Fig. 8C). As above, the CMV promoter-driven LacZ gene is isolated from pCMVß (Clontech; Fig. 8D; also Fig. 7D) as a 4.5kb EcoRI-SalI fragment and ligated with similarly digested pSP-C68-MU 0-1.3 DNA to yield pSP-C68-MU 0-1.3-CMVß (Fig. 8E).

For the initial step in the isolation of the map unit 9-16 region of C68, pGEM-3Z (Fig. 8F; also Fig. 7F) and pBS-C68-BamF (Fig. 8G) are double digested

with BamHI and SphI and the 293bp fragment from pBS-C68-BamF is ligated with the pGEM-3Z backbone to form pGEM-C68-MU9-10 (Fig. 8H). C68 map units 10-16.7 are isolated from pBS-C68 BamB (Fig. 8I) by digestion with XbaI, followed by filling in of the ends and digestion with BamHI. The 2.4 kb fragment is ligated with BamHI/EcoRV-digested pGEM-C68-MU9-10 to form pGEM-C68-MU9-16.7 (Fig. 8J). The C68 map unit 9-16.7 region is isolated from pGEM-C68-MU9-16 by digestion with EcoRI, filling in of the ends with Klenow and then digestion with HindIII. The 2.7 kb fragment is ligated with pSP-C68-MU 0-1.3-CMVß (Fig. 8E), digested with HindIII and PvuII to form the final plasmid, pC68-CMV-LacZ (Fig. 8K).

pC68-CMV-LacZ (Fig. 8K) thus contains C68 Ad mu 0 to 1.3, followed by the CMV promoter, an SD/SA, the LacZ gene, a SV40 poly A sequence and C68 Ad mu 9-16.7, as well as additional plasmid sequence. This plasmid is co-transfected into the E1-expressing cell line with another C68 Ad to produce by homologous recombination a recombinant chimpanzee adenovirus carrying the LacZ gene.

D. pBS-Notx2

The LacZ gene is removed from either pC1-CMV-LacZ (Fig. 7K) or pC68-CMV-LacZ (Fig. 8K) by digestion with NotI, and replaced by the coding sequence of any desired gene. This cloning step is facilitated by having the gene of interest flanked by NotI restriction sites, preferably with the upstream site in the 5' untranslated region of the gene.

Such a cloning vector is derived from pBluescript SK+ (Stratagene, La Jolla, CA) by digestion of SK+ with SalI, followed by filling in of the ends and

ligation with a synthetic 8bp NotI linker (New England Biolabs, Beverly, MA): GCGGCCGC.
CGCCGGCG

The resulting pBS-Notx2 shuttle vector (Fig. 4B) is thus designed to facilitate cloning of cDNAs into pC1-CMV-LacZ (Fig. 7K) and pC68-CMV-LacZ (Fig. 8K; see also Fig. 4A) as a NotI fragment. pBS-Notx2 has two NotI sites flanking a number of restriction sites suitable for cloning the cDNA to be expressed in the recombinant adenoviruses and the LacZ ORF from pBluescript is maintained, allowing blue/white screening of clones in pBS-Notx2.

E. Homologous Recombination with Helper Virus

To generate the recombinant adenoviruses from the plasmids described above, the appropriate E1-expressing packaging cell line, such as 293 cell line or a cell line of Example 4, is co-transfected with a replication defective C1 or C68 helper virus, or a left-end clipped C1 or C68 fragment, as appropriate. These helper viruses may be deleted of other non-essential genes. The infected cell line is subsequently transfected with an adenovirus vector as described above bearing the transgene of interest. Homologous recombination occurs between the helper and the plasmid, which permits the adenovirus-transgene sequences in the vector to be replicated and packaged into virion capsids, resulting in the recombinant adenovirus.

Transfection is followed by an agar overlay for 2 weeks, after which the viruses are plaqued, expanded and screened for expression of the transgene. See, for example, Figs. 10A-10D. Several additional rounds of plaque purification are followed by another expansion of the cultures. Finally the cells are harvested, a virus extract prepared and the recombinant chimpanzee adenovirus containing the desired transgene is

purified by buoyant density ultracentrifugation in a CsCl gradient. All of the above procedures are known to those of skill in the art.

F. Another C1 Recombinant Adenovirus

Another set of plasmids used to construct a C1 recombinant adenovirus is described as follows. Figs. 11A-11H illustrate the scheme employed to generate a unique restriction site in the left end of the C1 genome. A unique site is necessary in the procedure employed in generating a recombinant adenovirus, but C1 has no such site. There are two Spe-I restriction sites, including one at position 1733, within the E1B 21K coding region. To replace this Spe-I site with a unique Not-I site, plasmid pNEB-C1-BamG (Fig. 11A), containing the left end of the C1 genome, was digested with Spe-I and Asc-I, and ligated to the 6204 bp Spe-I/Asc-I fragment from the C1 genome (Fig. 11B). The resulting plasmid, pNEB-C1-AscI-B (Fig. 11C) is then digested with Spe-I, filled in with Klenow enzyme and ligated to the synthetic 8bp Not-I linker (Fig. 11D) described above, to yield pNEB-C1-AscI-B-NotI (Fig. 11E).

This plasmid is digested with Pac-I and Asc-I and the purified fragment is ligated overnight with the C1-Asc-I-A fragment (Fig. 11G). The ligation reaction is extracted with phenol:chloroform:iso-amyl alcohol, then chloroform, and then 3 μg of sheared salmon sperm DNA is added and the DNA is ethanol precipitated. The resuspended DNA is used to transfect 293 cells and DNA from viral plaques is tested for a Not-I site (11H).

G. GFP as a Transgene

Plasmids used to construct exemplary C68 expression plasmids containing the bacterial green fluorescent protein (GFP) gene are illustrated in Figs. 9A through 9G, respectively. To facilitate the cloning of the GFP gene into the chimp Adeno expression vectors,

pEGFP-1 (Fig. 9A, Clonetech, Palo Alto, CA) was digested with Sma-I and ligated to the previously described 8bp Not-I linker (Fig. 9B). The resulting plasmid, pEGFP-Notx2 (Fig. 9C) has the GFP gene flanked by Not-I sites.

The purified pEGFP-Notx2 Not-I fragment is ligated to Not-I digested pC1-CMV-LacZ (Figs. 7K and 9D) or pC68-CMV-LacZ (Figs. 8K and 9E) to yield the GFP expression vectors pC1-CMV-GFP (Fig. 9F) and pC68-CMV-GFP (Fig. 9G and Fig. 10A), respectively.

Example 6: Delivery of Transgene to Host Cell

The resulting recombinant chimpanzee adenovirus described in Example 5 above is then employed to deliver the transgene to a mammalian, preferably human, cell. For example, following purification of the recombinant C68-CMV-GFP virus of Example 5G, human embryonic kidney 293 cells and A549 cells were infected at an MOI of 50 particles per cell. GFP expression was documented 24 hours post-infection.

In vivo studies have tested the infectivity of the virus in murine liver (tail vein injection), lung (intratracheal injection) and muscle (intramuscular injection). Preliminary data indicate that the C68-CMV-GFP recombinant virus transduces all three tissues, and GFP expression can be detected.

When administered *in vivo*, a less severe immune response is produced by the human immune system (which is naive to the chimpanzee adenovirus sequences) than to a human adenovirus construct, thereby permitting subsequent administration of the same or another vector.

All references recited above are incorporated herein by reference. Numerous modifications and variations of the present invention are included in the scope of the above-identified specification and are expected to be obvious to one of skill in the art. Such

modifications and alterations to the compositions and processes of the present invention, such as selections of different minigenes or selection or dosage of the vectors or immune modulators are believed to be within the scope of the claims appended hereto.

SEQUENCE LISTING

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(C) OPERATING SYSTEM: PC-DOS/MS-DOS
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35524 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CCATCATCAA TAATATACCT TAAACTTTTG GTGCGTGTTA ATATGCAAAT GAGGCGTTTG 60

AATTTGGGGA GGGTGAAAGG TGATTGGCTG TGGGGACGGC GACCGTTAGG GGCGGGGCGG 120

GTGACGTTTT GATGACGTGG TCGTGAGGCG GAGTTGGTTT GCAAGTTCTC GTGGGAAAAG 180

TGACGTCAAA CGAGGTGTGG TTTGAACACG GAAATACTCA ATTTTCCCGC GCTCTCTGAC 240

AGGAAATGAT GTGTTTTTGG GCGGATGCAA GTGAAAATTC CTCATTTTCG CGCGAAAACT 300

AAATGAGGAA GTGAATTTCT GAGTAATTTC GTGTTTATGA CAGGGTGGAG TATTTACCGA 360

GGGCCGAGTA GACTTTGACC GATTACGTGG AGGTTTCGAT TACCGTGTTT TTCACCTAAA 420

TTTCCGCGTA CGGTGTCAAA GTCCTGTGTT TTTACGTAGG TGTCAGCTGA TCGCTAGAGT 480

ATTTAAACCT GACGAGTTCC GTCAAGAGGC CACTCTTGAG TGCCAGCGAG AAGAGTTTTC 540

TCCTCCGCAC TGCGAGTCAG ATCTCCACTT TGAAAATGAG ACACCTGCGC TTCCTGTCCC 600

AGGAGATAGT CTCCACTGAG ACTGGGAATG AAATACTGCA ATTTGTGGTA AATACACTGA 660

TGGGAGACGA TCCAGAGCCG CCTGAGCCAC CTTTTGATCC TCCTACGCTT CATGAATTAT 720

ATGATTTAGA GGTAGACGGA CCGGAGGACC CTAATGAAAA CGACGTGAAT GGGTTTTTTA 780

CTGATTCTAT GTTATTAGCT GCTAATGAGG GAGTGGATTT AGACCCACCT TCTGGAACTT 840

TTGATACTCC AGGGGTGATT GTGGAAAGCG ACATAGATGG GAAAAATTTA CCTGATTTGG 900

GTGCTGCTGA ATTGGACTTA TACTGCTATG AAGAGGGTTT TCCTCAGAGT GATGATGAAG 960

ATGTGGAGAA TGAGCAGTCA ATTCAGACCG CCGCGGGTGA GGGAGTGAAA GCTGCCAGTG 1020

ATGGTTTTAA GTTGGACTGT CCGGTGCTTC CTGGACATGG CTGTAAGTCT TGTGAATTTC 1080

ACAGGAAAAA TACTGGAGTA AAAGAAATAT TATGCTCGCT TTGTTATATG AGAGCGCATT 1140

GCCACTTTAT TTACAGTAAG TGTGTTTAAA GTTAAATTTA AAGGAACAGT AGCTGTTTTA 1200

ATAACTCTTG AATGGGTGAT TTATGTTTTG CTGATTTTTA TAGGTCCTGT GTCTGATGCT 1260

GATGAATCGC CTTCTCCTGA TTCAACTACC TCACCTCCTG AAATTCGGGC ACCCGTTCCT 1320

GCAAACGTAT GCAAGCCCAT TTCTGTGAAG CTTAAGCCTG GGAAACGCCC TGCTGTGAAT 1380

AAACTTGAGG ATTTGCTGGA GGGTGTGGAT GAACCTTTGG ACTTGTGTAC CCGGAAAATA 1440

CCAAGGCAAT GAGTGCTCCG CACCTGTGTT TATCTAATGT GACGTCACTG TTTTTGTGAG 1500

AGTGTCATGT AATAAAATTA TGTCAGCAGC TGAGTGTTTT ATTGTTTATT GGGTGGGACT 1560

TGGGATATAT AAGTAGGAGC AGACCTGTGT GGTTAGCTCA CAGCAGCTTG CTGCCATCCA 1620

TGGAGGTTTG GGCCATATTG GAAGATCTTA GGCAGACTAG GCAACTGCTA GAAAACGCCT 1680

CGGACAGAGT CTCTGGTCTT TGGAGATTCT GGTTCGGTGG TGATCTAGCT AGACTAGTCT 1740

TTAGGATAAA GCAGGATTAC AGGCAAGAAT TTGAAAAGTT ATTGGACAAC TGTCCAGGAC 1800

TTTTTGAAGC TCTTAACTTG GGCCACCAGG CTCATTTTAA GGAGAAGGTT TTATCAGTTT 1860

TGGATTTTTC TACCCCTGGT AGAACTGCTG CTGCTGTAGC TTTCCTTACA TTTATATTTG 1920

ATAAATGGAT CCCACAGACC CACTTCAGCA AGGGATACGT TTTGGATTTC ATAGCAGCAG 1980

CTTTGTGGAG AACATGGAAG GCTCGCAGGA TGAGGACAAT CTTAGATTAC TGGCCAGTAC 2040

AGCCTCTGGG TGTAGCAGGG ATCCTGAGAC ACCCACCGAC CATGCCAGCG GTTTTGGAGG 2100

AGGTGCAACA AGAGGACAAT CCGAGAGCCG GCCTGGACCC TCCGGTGGAG GAGGCGGAGG 2160

AGTAGCTGAC TTGTTTCCTG AACTGCGACG GGTGCTTACT AGATCTACAA CCAGTGGGCG 2220

GGACAGGGGC ATTAAGAGGG AAAGGAATCC TAGTGGAACT AATCCCAGAT CTGAGTTGGC 2280

TTTAAGTTTG ATGAGTCGCA GACGTCCTGA AACTATATGG TGGCATGAGG TTCAGAATGA 2340

GGGCAGGGAT GAAGTATCAA TATTGCAAGA GAAATATTCT CTAGAACAGG TGAAAACATG 2400

TTGGTTGGAG CCTGAGGATG ATTGGGAGGT TGCCATTAGG AATTATGCCA AGATAGCTTT 2460

GAGGCCTGAT AAATTGTACA GAATTACTAA ACGGATTAAT ATTAGAAATG CATGCTATAT 2520

ATCAGGGAAT GGGGCTGAGG TAGTGATAGA CACTCAGGAC AGAACAGTTT TTAGATGCTG 2580

TATGATGGGT ATGTGGCCAG GGGTGATTGG CATGGAGGCG GTAACCTTTA TGAATGTAAA 2640

GTTTAGAGGG GATGGGTATA ATGGTGTGGT TTTTATGGCT AATACTAAAT TGATTTTGCA 2700

TGGTTGTAGC TTTTTTGGTT TTAATAATAT ATGTGTGGAA GCTTGGGGGC AGGTCAGTGT 2760

AAGAGGCTGT AGTTTCTATG CATGCTGGAT TGCAACATCA GGCAGGACCA AGAGTCAATT 2820

GTCTGTGAAG AAATGTATGT TTGAGAGATG TAACCTGGGC ATACTAAATG AAGGAGAAGC 2880

CAGAGTCAGC CACTGTGCTT CTTCCGAAAC TGGCTGTTTC ATGTTGATGA AGGGAAATGC 2940

CAATGTGAAA CATAATATGA TCTGCGGACC CTCAGATGAC AGGCCTTATC AGATGCTGAC 3000

ATGTGCTGGC GGACATTGCA ATATGCTGGC TACCGTGCAT ATTGTTTCTC ACCCACGCAA 3060

GAAATGGCCT GTTTTGGAAC ATAATGTGAT GACCAAATGT ACCATGCACG TAGGTGGACG 3120

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ATGG 35524

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36519 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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AACGCGCACA AAAAGTTTGA GGTATATTAT TGATGATGG 36519

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8299 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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AGCGAGGAAG CGGAAGAGC 8299

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GCAGGTACCG CGAGTCAGAT CTACAC 26

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CTGTCTGAGC TAGAGCTC 18

WHAT IS CLAIMED IS:

1. A vector comprising a chimpanzee adenovirus DNA sequence and a selected heterologous gene operatively linked to regulatory sequences which direct expression of said gene in a heterologous host cell.

2. The vector according to claim 1 wherein said chimpanzee adenovirus sequence comprises at least 5' and 3' cis-elements necessary for replication and virion encapsidation, said cis-elements flanking said selected gene and regulatory sequences.

3. The vector according to claim 1 wherein said chimpanzee adenovirus sequence has a deletion in all or a part of the E1 gene.

4. The vector according to claim 1 wherein said chimpanzee adenovirus sequence comprises the sequence of SEQ ID NO: 1 or a fragment thereof.

5. The vector according to claim 1 wherein said chimpanzee adenovirus sequence comprises the sequence of SEQ ID NO: 2 or a fragment thereof.

6. A host cell transfected with the vector of claim 1.

7. A human cell that expresses a selected gene introduced therein through transduction of the vector of claim 1.

8. A non-simian mammalian cell line that expresses a chimpanzee adenovirus gene.

9. The cell line according to claim 8 wherein said gene is an adenovirus E1 gene or a functional fragment of said E1 gene.

10. The cell line according to claim 8 wherein said chimpanzee adenovirus gene is obtained from the sequence of SEQ ID NO: 1.

11. The cell line according to claim 8 wherein said chimpanzee adenovirus gene is obtained from the sequence of SEQ ID NO: 2.

12. A pharmaceutical composition comprising a recombinant adenovirus vector in a pharmaceutically acceptable carrier, said vector comprising a chimpanzee adenovirus DNA sequence and a selected heterologous gene operatively linked to regulatory sequences which direct expression of said gene in a host cell.

13. A method for delivering a heterologous gene to a mammalian cell comprising introducing into said cell an effective amount of the vector of claim 1.

14. A method for producing a selected gene product comprising infecting a mammalian cell with the vector of claim 1, culturing said cell under suitable conditions and isolating and recovering from said cell culture the expressed gene product.

15. The use of a vector comprising a chimpanzee adenovirus DNA sequence and a selected heterologous gene encoding an antigen of an infective agent operatively linked to regulatory sequences which direct expression of said gene in the production of a medicament for eliciting an immune response in a mammalian host against said infective agent.

16. The use of a vector comprising a chimpanzee adenovirus DNA sequence and a selected heterologous therapeutic gene operatively linked to regulatory sequences which direct expression of said gene in the production of a medicament for treating a patient having an acquired or inherited genetic defect.

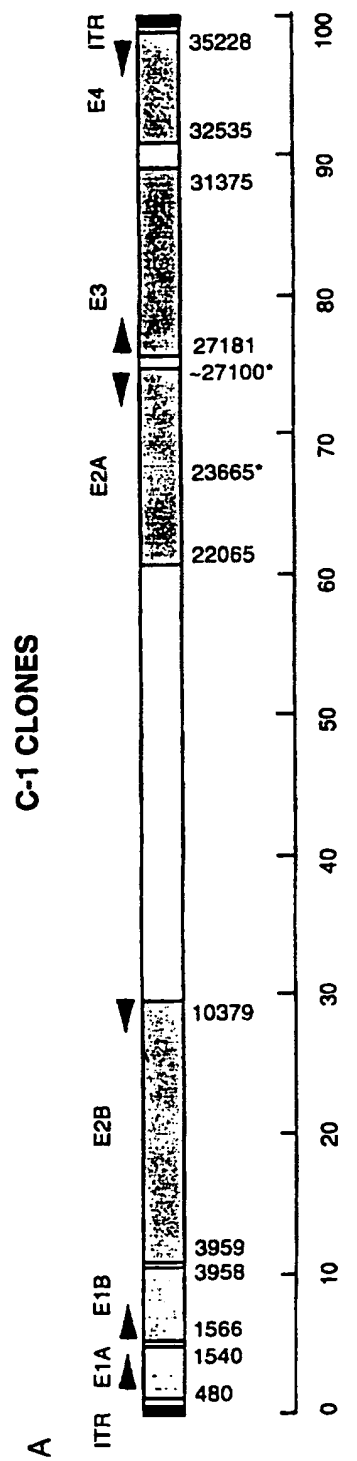


Fig. 1A

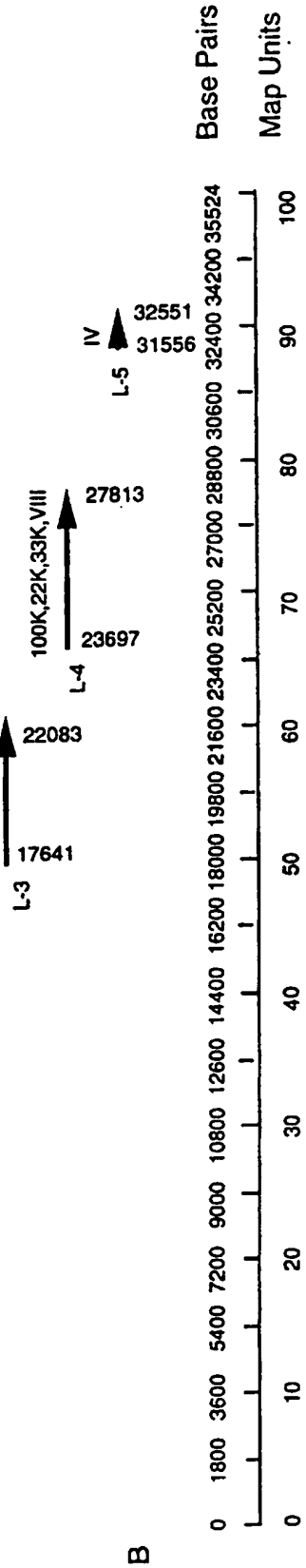


Fig. 1B

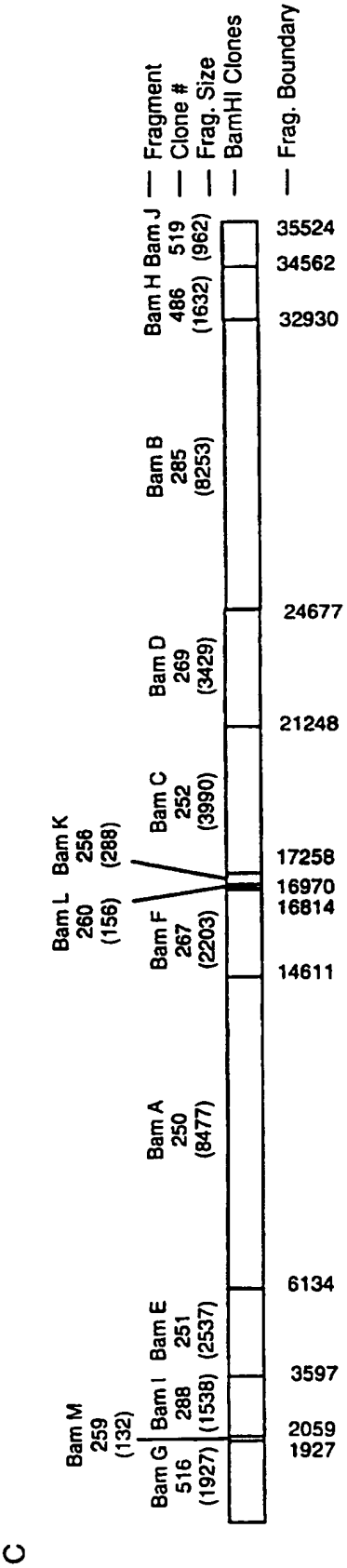


Fig. 1C

Human Serotype Sub-group Chimp Virus	C1 vs C68		Ad-4 E C1	 C68	Ad-5 C C1	 C68	Ad-7 B C1	 C68	Ad-12 A C1	 C68	Ad-40 F C1	 C68
Protein C1/C68 aa												
E1 and pIX regions												
E1A 6/11K	58/101		26[a]		41	52[a]	29	14[a]	81	26[a]	12	NH[a]
E1A 25K	231/226		55		56	91	33	26	82	60	36	37
E1A 28K	262/257		57		57	92	34	34	83	61	37	40
E1B 21K	181/186		60		49	68[b]	48	46	94	61	39	38
E1B 55K	495/498		74				53	57	88	73	46	46
E1B 8.3K	91/102		54				21	29	85	53	21	25
pIX	139/143		80				52	48	96	80	56	51
E2 and IVa2 Regions												
E2A DBP	516/513		78		76	93	53	53	86	76	45	49
E2B pTP	643/628		91		90	94	81	80	96	90	75	76
E2B pol	1121/1125		90		83	92	75	76	96	90	72	72
IVa2	448/448		93				82	82	96	92	76	77
E3 Region												
E3A#1	106/106		78				52	58	96	78	66	70
E3A#2	146/209		33[a]				NH	NH	80	34	NH	NH
E3A#3	172/176		60				38	32	75	60	NH	NH
E3Hyp	184/204		26				NH	NH	73	34	NH	NH
E3Hyp	188/204		31				NH	NH	82	31	NH	NH
E3Hyp	103/295		NH				NH	NH	48[a]	NH	NH	NH
E3B#4	91/ 91		71				47	48	92	77	44	41
E3B#5	134/143		54				34	32	75	49	27	25
E3B#6	135/135		79				52	54	91	80	52	52
E4 Region												
E4	123/124	orf-1	70				42	45			44	50
E4	129/129	orf-2	64				32[c]	31[c]			30	31
E4	117/117	orf-3	84				49	52			65	67
E4	124/121	orf-4	62				45	56			40	45
E4	303/301	orf-6	76				57	63			50	51
E4	83/ 64	orf-7	60				42	55			49	42
Late Region												
L1 16.6K	139/139	AgnoP	76				45	47	88	74	28	25
L1 52/55K	389/391		85				69	69			71	70
L1 IIIa	586/592		85				76	79			75	66
L2 III	564/534	Penton	82				70	72	85	83[d]	72	76
L2 pVII	192/193		91		87	96	73	70			76	74
L2 pV	353/343	M.Core	84				58	61			63	67
L2 pVU	76/ 77		91				69	73			65	64
L3 pVI	250/242		79				65	68			66	58
L3 II	956/933	Hexon	86		85	88	79	78	86	85	76	79
L3 23K	207/206	EndoPr	89		78	88	75	76	93	87	79	80
L4 100K	828/804		80				62	65			61	64
L4 22K	197/188	Morph	72				43	40			36	38
L4 33K	231/222		76				44	44			NH	NH
L4 pVIII	227/227	Hex As	92		95	90[e]	79	79	86	78[f]	78	79
L5 IV	322/425	Fiber	24[a]		27[a]	90	19[a]	36[a]	66	26[a]	18[a]	28[a]

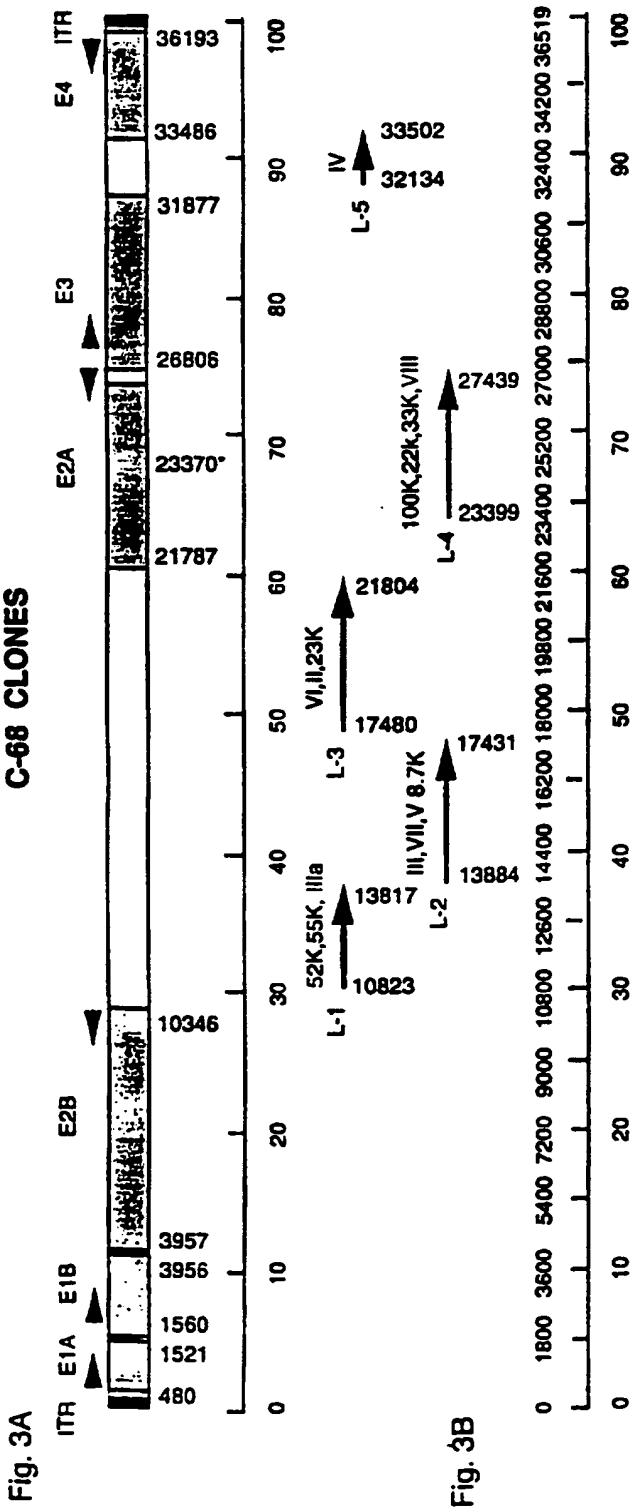


Fig. 3A

Fig. 3B

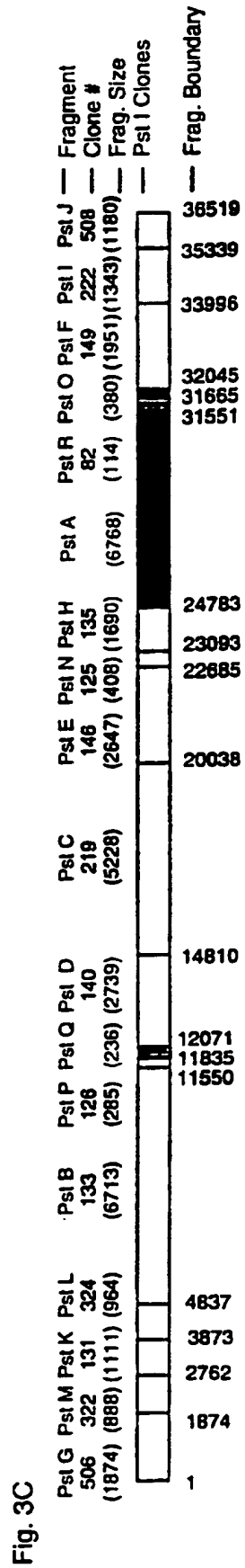


Fig. 3C

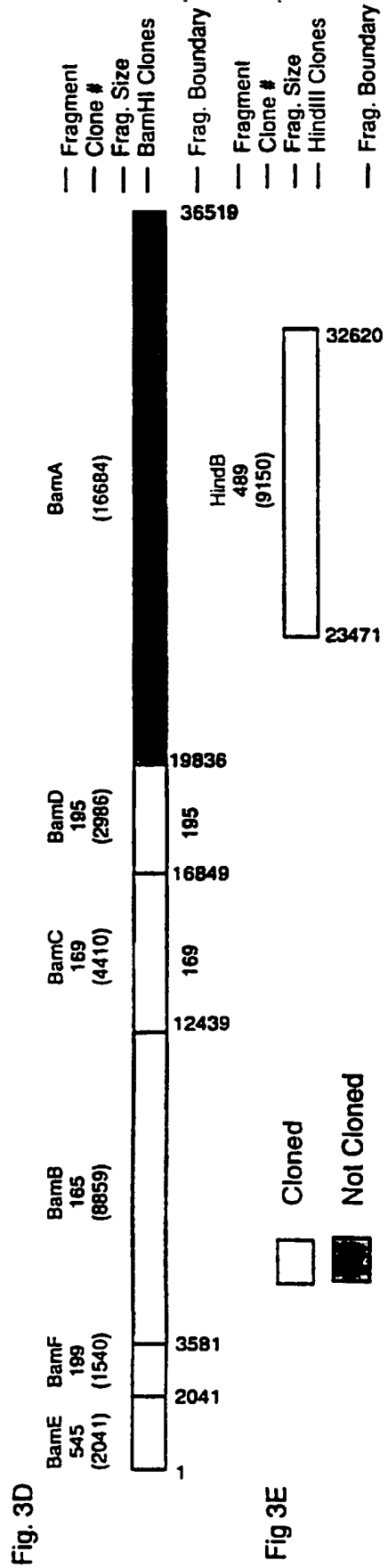


Fig. 3D

Fig 3E

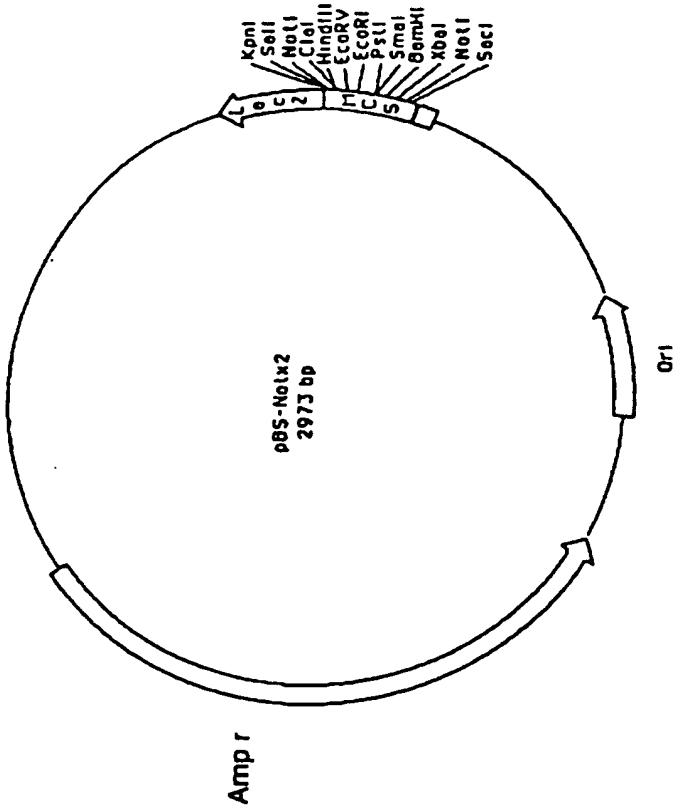

KpnI
SalI
NotI
ClaI
HindIII
EcoRV
EcoRI
PstI
SmaI
BamHI
XbaI
NotI
SacI
Lac Z
pBS-Notx2
2973 bp
Ori
Amp r

Fig. 4B

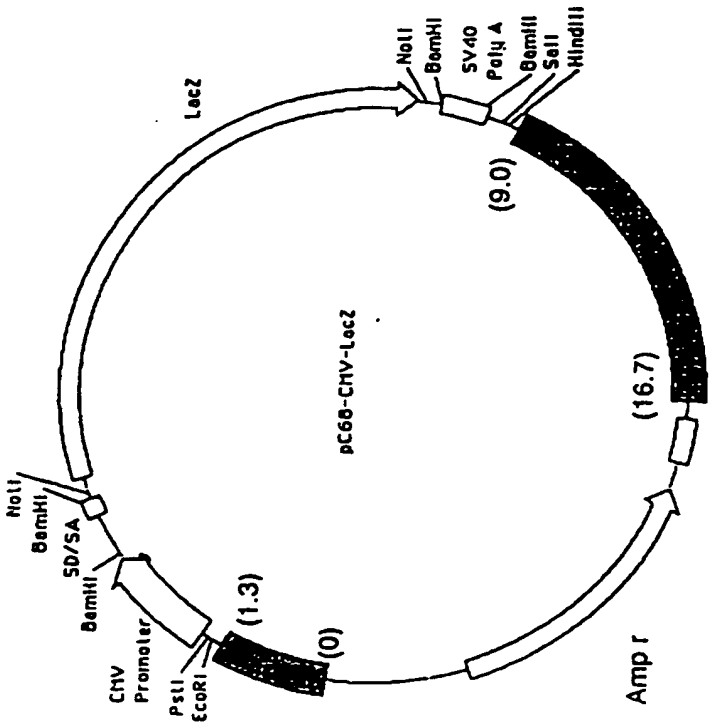

Lac2
NotI
BamHI
SV40
Poly A
BamHI
SalI
HindIII
(9.0)
(16.7)
pC66-CHV-Lac2
NotI
BamHI
SD/SA
BamHI
CHV
Promoter
PstI
EcoRI
(1.3)
(0)
Amp r

Fig. 4A

C68 E1 Expression Plasmid

Fig. 5A

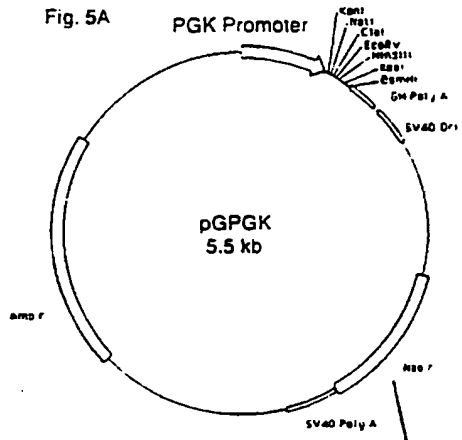


Fig. 5B

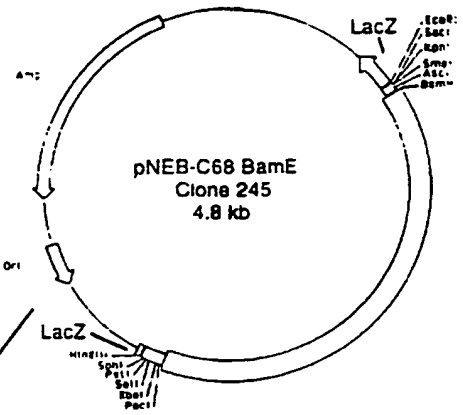
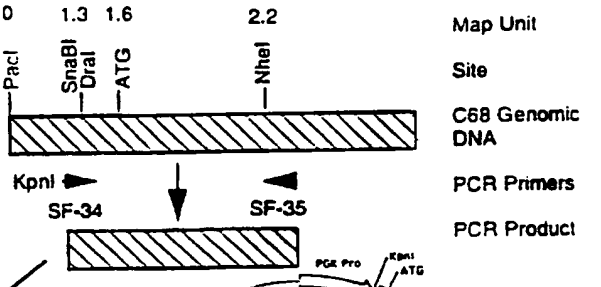


Fig. 5D



BamHI
HindIII

KpnI
NheI

Fig. 5C

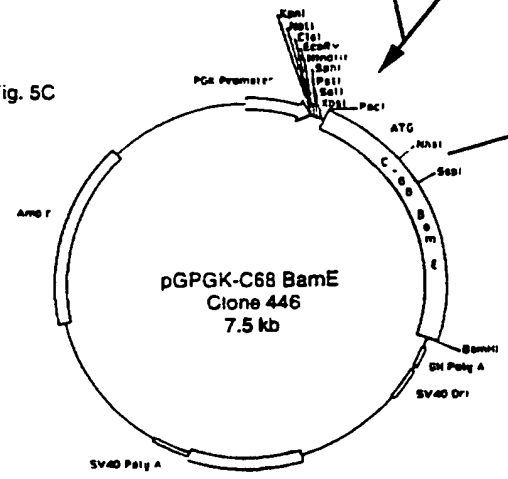
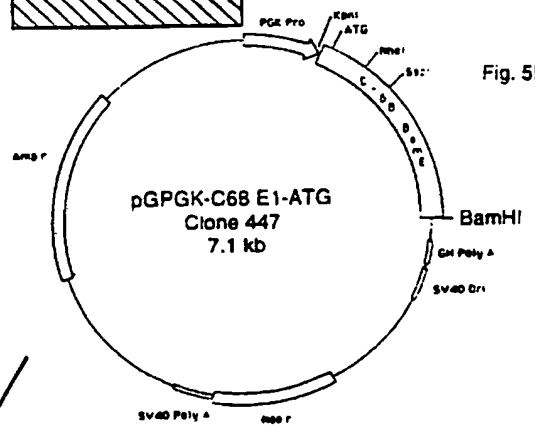


Fig. 5E



BamHI

Fig. 5F

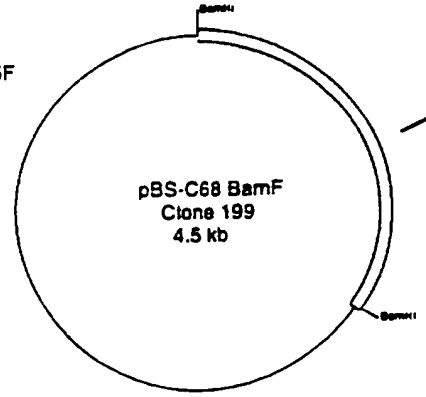
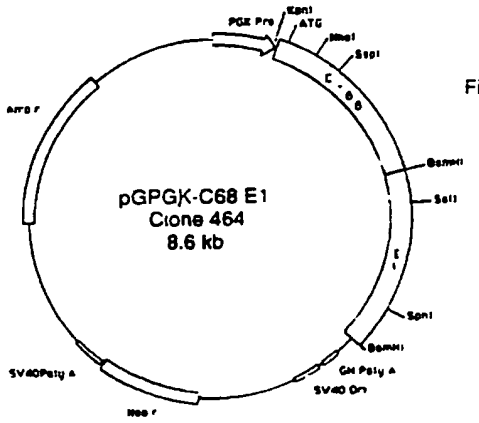


Fig. 5G



C1 E1 Expression Plasmid

Fig. 6A

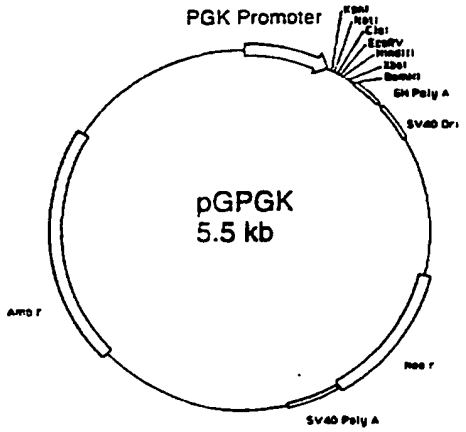
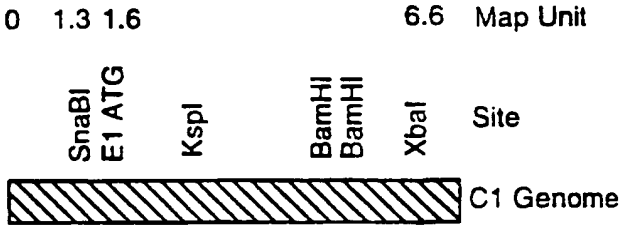


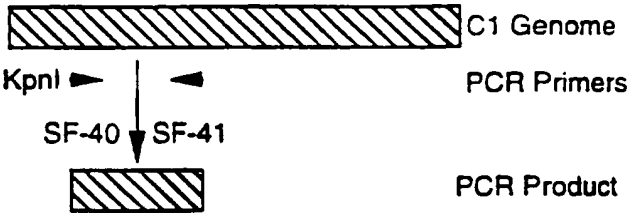
Fig. 6B



SnaBI
XbaI

EcoRV
XbaI

Fig. 6C



KpnI
KspI

Fig. 6D

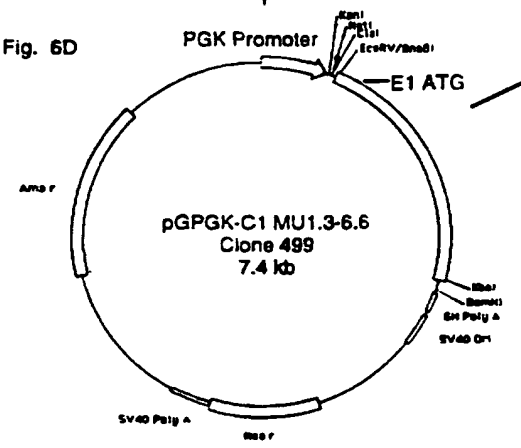
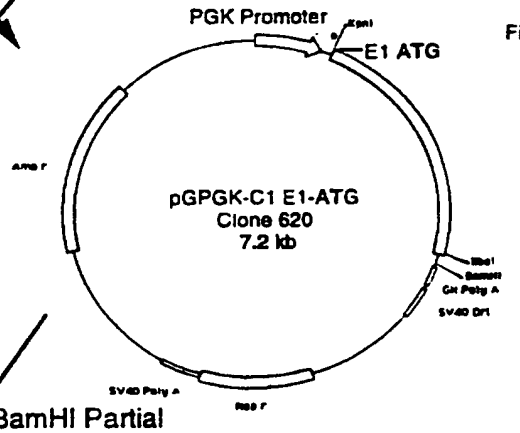


Fig. 6E



BamHI
XbaI

BamHI Partial
XbaI

Fig. 6F

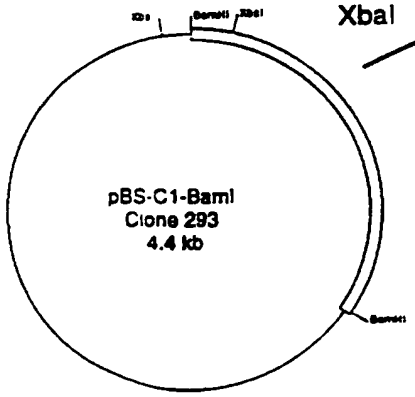
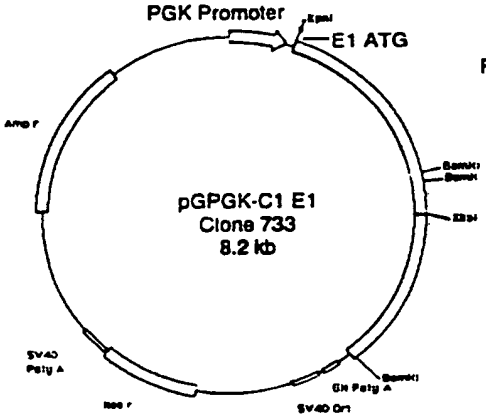
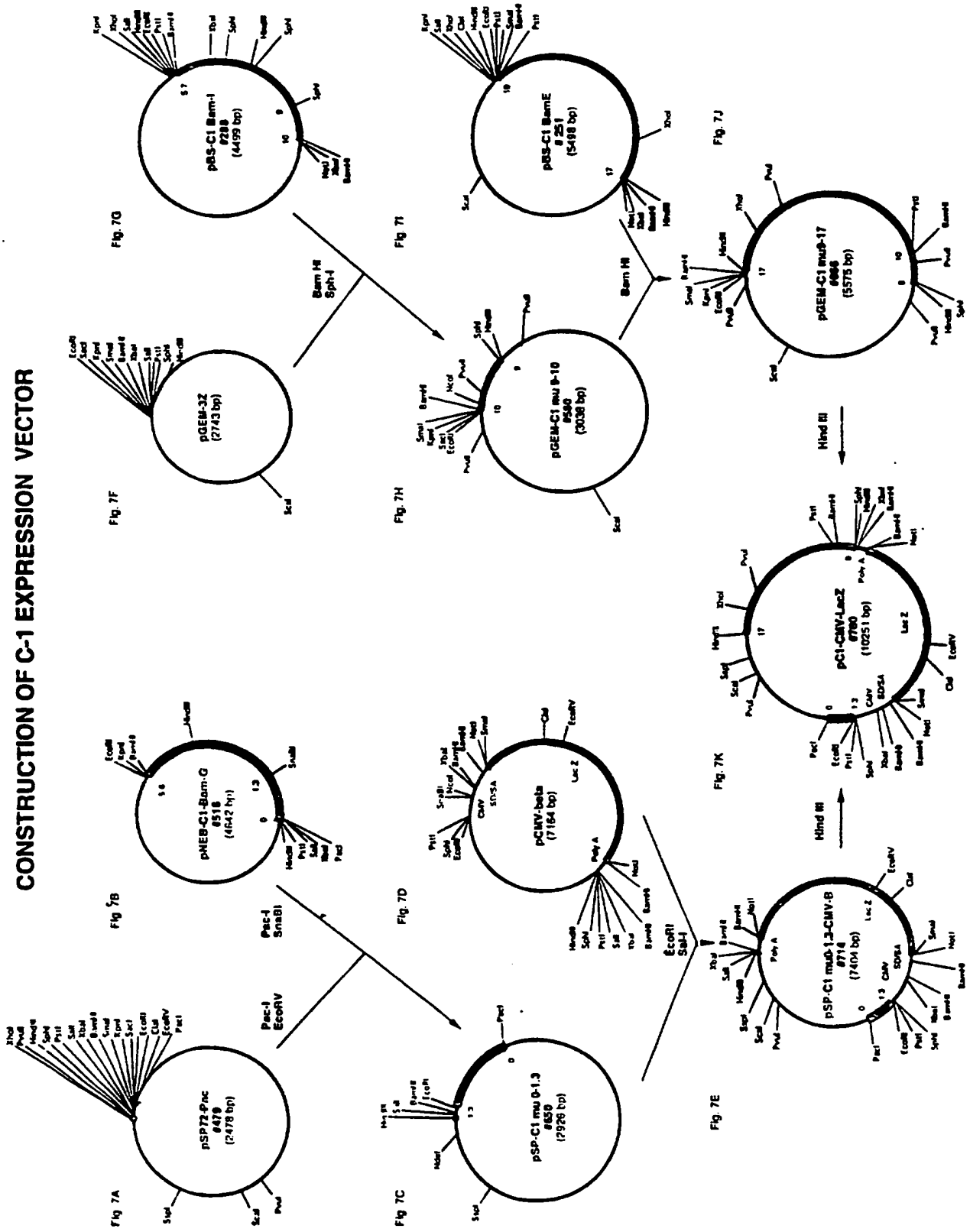
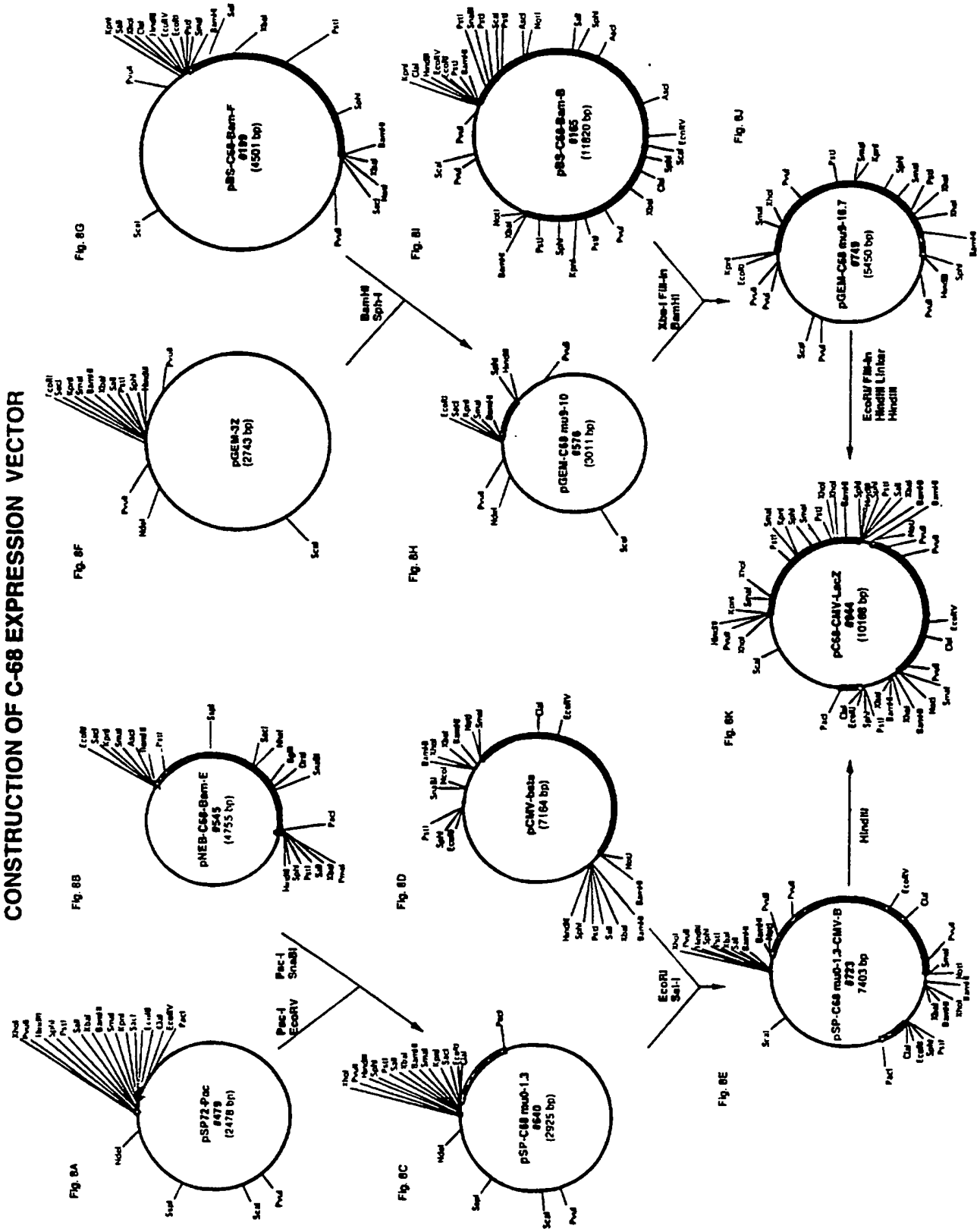


Fig. 6G




CONSTRUCTION OF C-1 EXPRESSION VECTOR
pSP72-Pac #419 (2478 bp)
pNEB-C1-Bam-G #518 (4642 bp)
pGEM-32 (2743 bp)
pBS-C1 Bam-I #288 (4499 bp)
pSP-C1 mu 0-1.3 #650 (2926 bp)
pCMV-beta (7164 bp)
pBS-C1 BamE #251 (5498 bp)
pGEM-C1 mu 6-10 #560 (3038 bp)
pSP-C1 mu0-1.3-CMV-B #714 (7404 bp)
pC1-CMV-LacZ #700 (10251 bp)
pGEM-C1 mu6-17 #666 (5575 bp)
Pac-I EcoRV
Pac-I SnaBI
Bam HI Sph-I
EcoRI Sal-I
Bam HI
Hind III
Hind III

CONSTRUCTION OF C-68 EXPRESSION VECTOR



CONSTRUCTION OF GFP EXPRESSION VECTORS

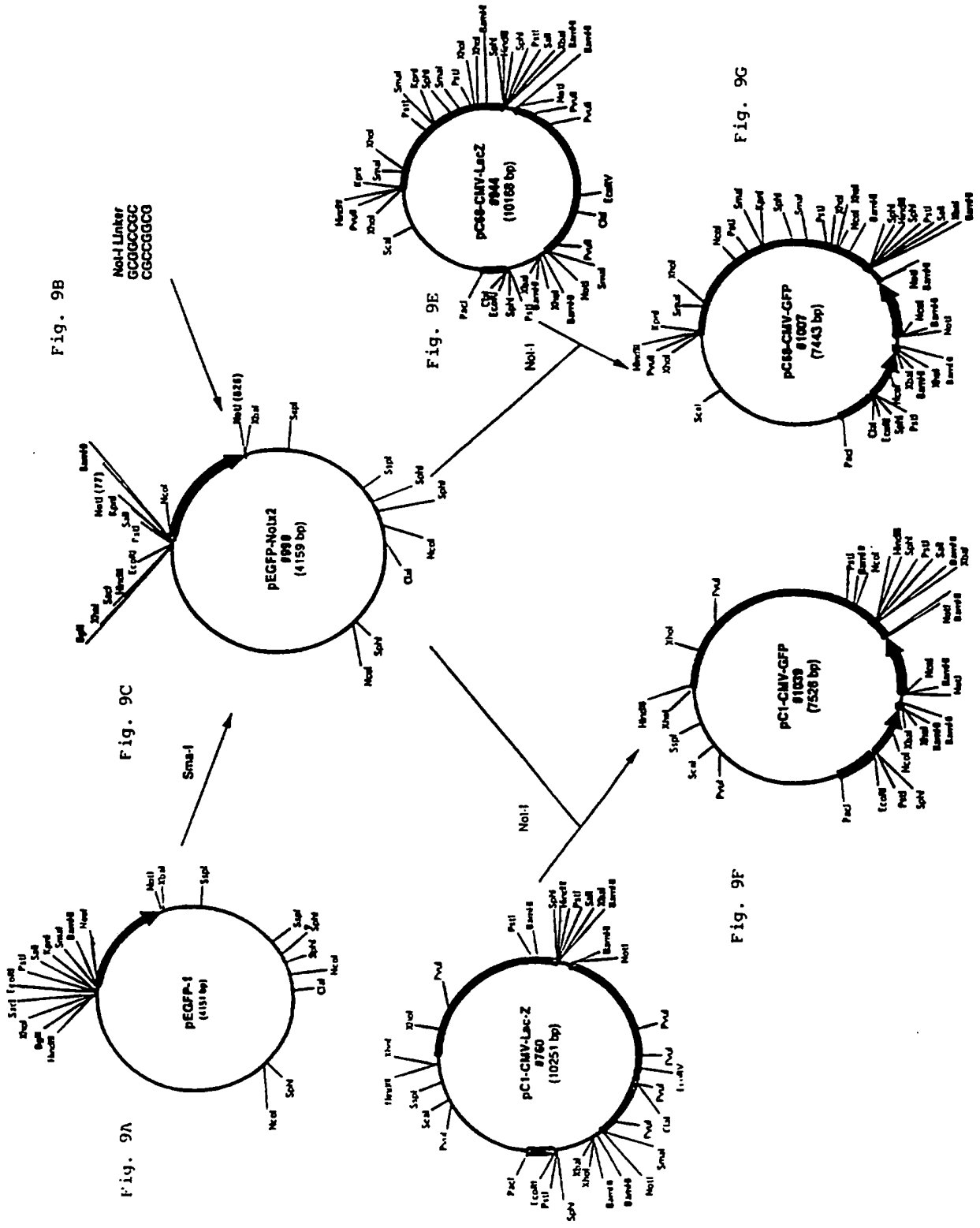


Fig. 9A

Fig. 9B

Fig. 9C

Fig. 9D

Fig. 9E

Fig. 9F

Fig. 9G

GENERATION OF RECOMBINANT C68-CMV-GFP VIRUS BY HOMOLOGOUS RECOMBINATION

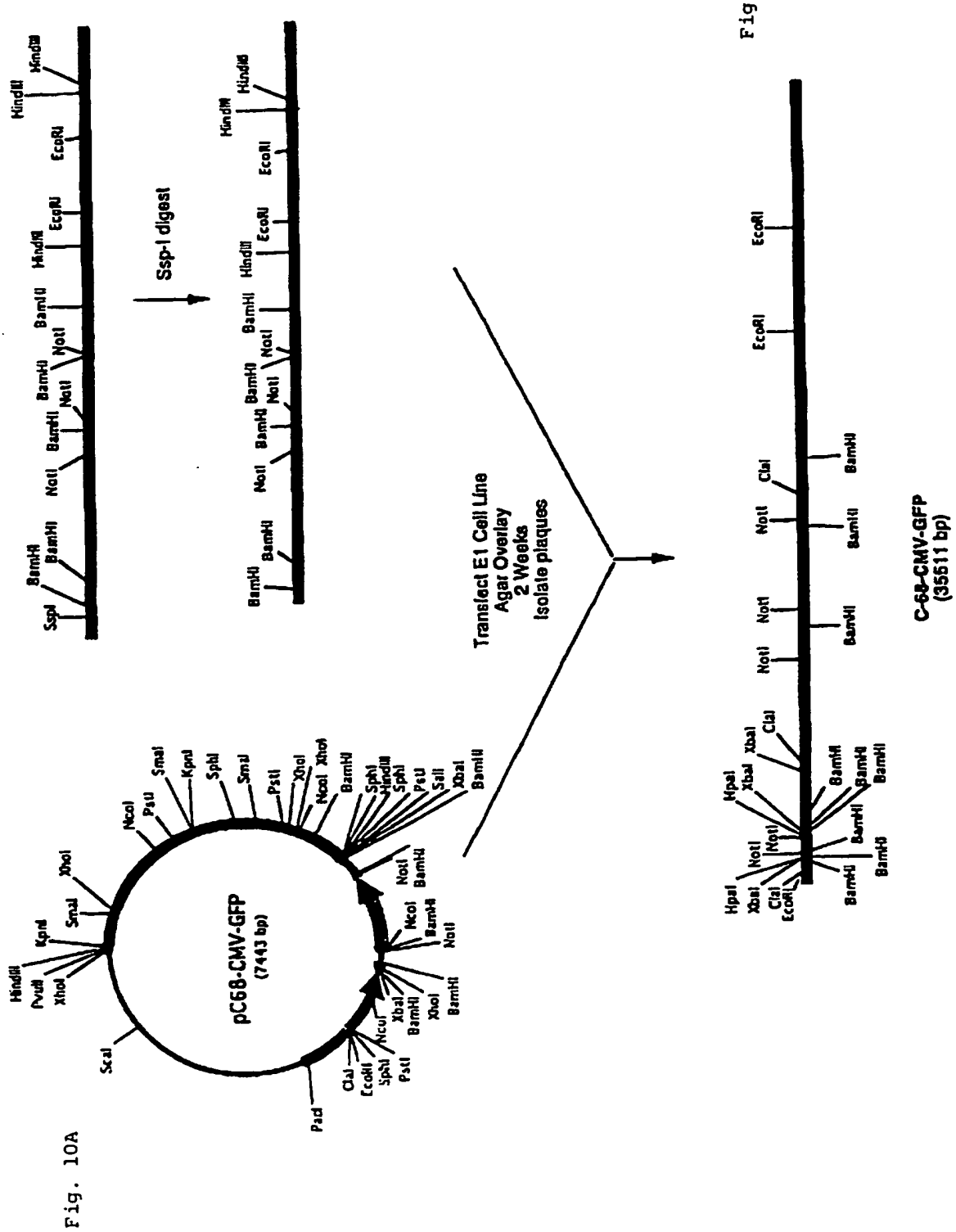
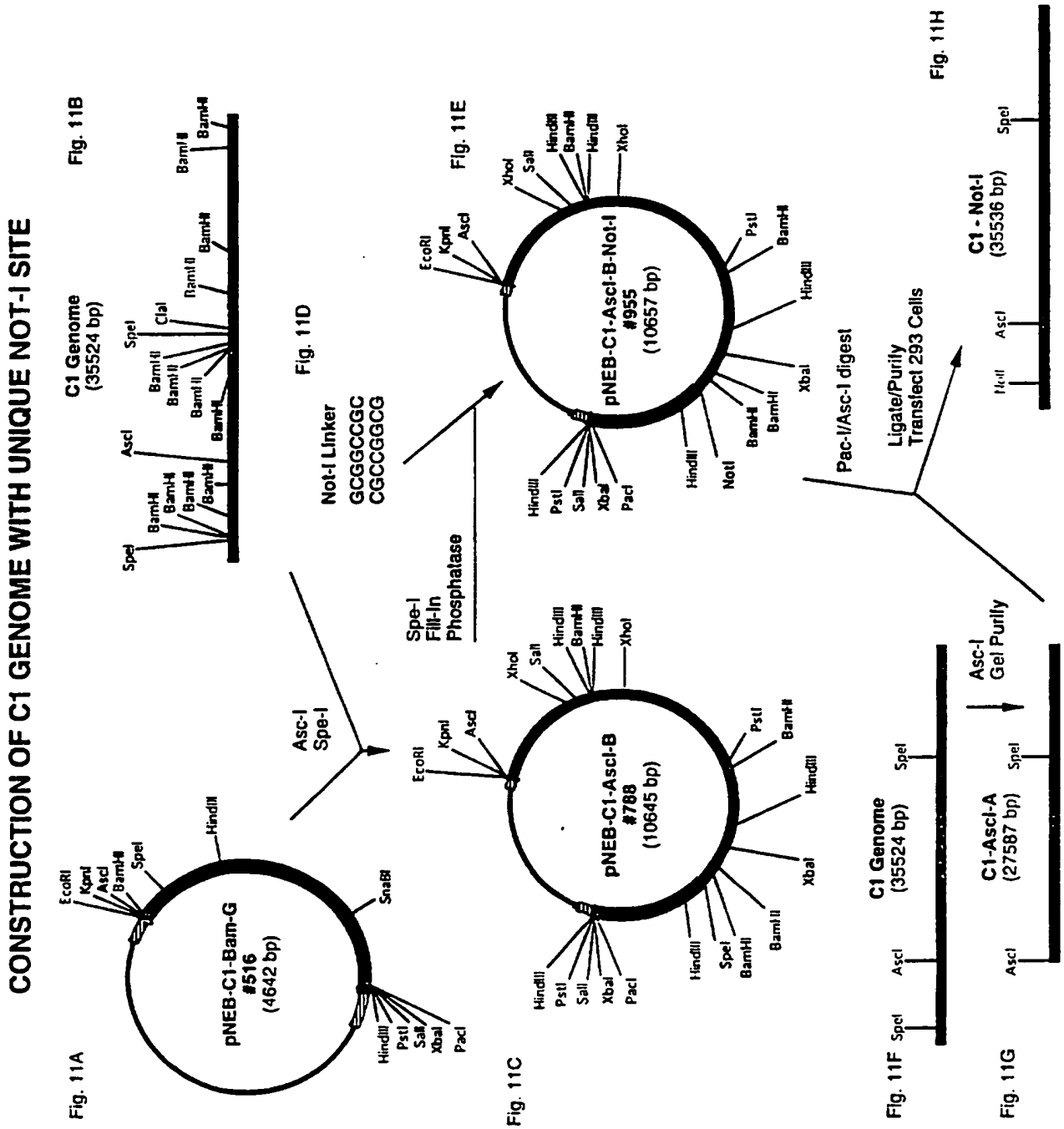


Fig. 10A

Fig. 10B

Fig. 10C

Fig. 10D


CONSTRUCTION OF C1 GENOME WITH UNIQUE NOT-I SITE
pNEB-C1-Bam-G
#516
(4642 bp)
EcoRI
KpnI
AscI
BamHI
SpeI
HindIII
SnaBI
HindIII
PstI
SalI
XbaI
PacI
Fig. 11A
C1 Genome
(35524 bp)
Fig. 11B
Asc-I
Spe-I
Not-I Linker
GCGGCCGC
CGCCGGCG
Spe-I
Fill-In
Phosphatase
Fig. 11D
pNEB-C1-AscI-B
#788
(10645 bp)
Fig. 11C
pNEB-C1-AscI-B-NotI
#955
(10657 bp)
Fig. 11E
Pac-I/Asc-I digest
Ligate/Purify
Transfect 293 Cells
C1 - Not-I
(35536 bp)
Fig. 11H
C1 Genome
(35524 bp)
Fig. 11F
C1-AscI-A
(27587 bp)
Asc-I
Gel Purify
Fig. 11G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/15694

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/86 C12N5/10 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 26914 A (RHÔNE-POULENC RORER S.A.) 24 November 1994 see page 2, line 33 - page 3, line 26 ---	1-3,6-9, 12-16
Y	A.H.KIDD ET AL.: "Human and simian adenoviruses: Phylogenetic interferences from analysis of VA RNA genes" VIROLOGY, vol. 207, no. 1, 20 February 1995, ORLANDO US, pages 32-45, XP002052836 see table 2 --- -/--	1-3,6-9, 12-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 1998	11.02.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cupido, M

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/15694

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R. WIGAND ET AL.: "Chimpanzee adenoviruses are related to four subgenera of human adenoviruses" INTERVIROLOGY, vol. 30, no. 1, January 1989 - February 1989, pages 1-9, XP002052837 cited in the application see page 1; table 4 -----	1-16

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/15694

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claim 13, insofar an in vivo method is concerned, is directed to a method of treatment of the human oranimal body , the search has been carried out and based on the alleged effects of the vector.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/15694

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9426914 A	24-11-94	FR 2705361 A	25-11-94
		AU 6787894 A	12-12-94
		BR 9406720 A	06-02-96
		CA 2163256 A	24-11-94
		CN 1124040 A	05-06-96
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		FI 955552 A	27-12-95
		HU 73465 A	28-08-96
		JP 8510122 T	29-10-96
		NO 954466 A	07-11-95
		PL 311660 A	04-03-96
		SK 144795 A	03-04-96
		ZA 9403358 A	16-01-95